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New Approaches in Asymmetric Rhodium-catalyzed Hydrogenations with Monodentate Phosphoramidites

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voor opa

Contents

Chapter 1 Introduction

Chapter 2 Catechol-based Phosphoramidites

Chapter 4 Monodentate Diamidophosphite Ligands

Chapter 5 Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Using a Mixed Ligand Approach

Chapter 6 Rhodium-catalyzed Asymmetric Hydrogenation of β²-Dehydroamino acids

Chapter 7 Phenol-based Phosphoramidites

Chapter 1
Introduction

This chapter gives an introduction to chirality and asymmetric catalysis. Recent trends in asymmetric hydrogenation with monodentate phosphoramidites ligands are also discussed.

1.1 Chirality

1.1.1 Introduction to chirality

Molecules are spatial structures of a collection of atoms. One of the most abundant atoms in nature is carbon (C). Carbon atoms in a molecule can possess four substituents. In 1874 Le Bell and Van 't Hoff proposed, independently, that the four substituents around a carbon atom are positioned in the corners of a tetrahedral structure.[1] A consequence of this spatial arrangement is that there are two different forms possible if a carbon has four *different* substituents. These two different structures are mirror images and not superimposable. These molecules are called asymmetric or chiral (Greek; Χειρ (cheir) = hand). The two mirror images are called enantiomers (Greek; εναντιος (enantios) = opposite) (Figure 1.1).

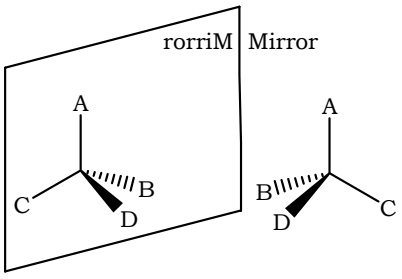


Figure 1.1: A pair of enantiomers: mirror images of a chiral molecule.

1.1.2 Isomers

Isomers are molecules with the same molecular formula but with different 3-dimensional structures (Figure 1.2). Two main classes of isomers can be distinguished; constitutional isomers and stereoisomers.[2] Stereoisomers can be divided in configurational and conformational isomers, where members of the latter class can be interconverted by rotation around a single bond. The former group can be subdivided in optical and geometric isomers. Enantiomers are part of the optical isomers, together with the diastereomers. As discussed before, enantiomers are mirror images of each other which are not superimposable by rotation or translation, due to a stereogenic carbon

atom. Diastereomers are chiral molecules which possess more than one stereogenic carbon atom. Almost all of the physical and chemical properties of enantiomers are identical,* which makes it difficult to distinguish between one and the other. On the other hand, diastereomers posses different physical and chemical properties, which makes it easier to differentiate them from each other.

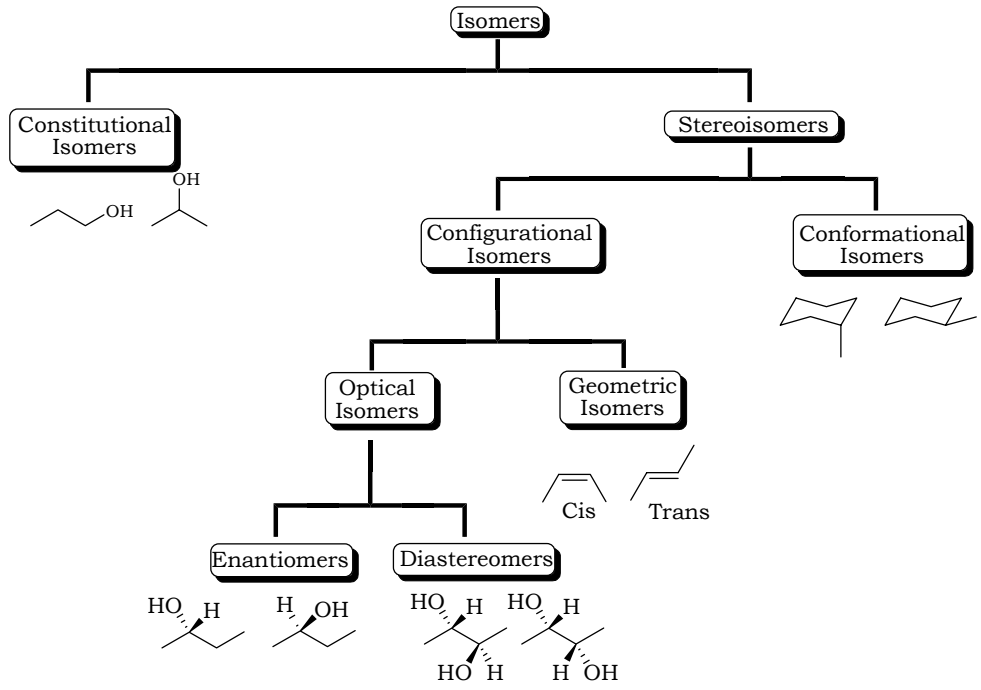
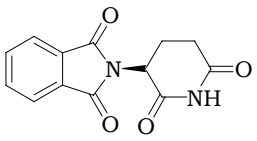


Figure 1.2: Classification of isomers.

1.1.3 Chirality in daily life



Softenon (thalidomide) (**1**)

Chirality is an important aspect of life, since for example most natural α-amino acids occur only as a single enantiomer. Another striking example of the effects of chirality is the so-called Softenon

* Only the interaction with other chiral molecules and the optical activity of the enantiomers are different.

(alias Thalidomide) (**1**) disaster. This medicine was administered to pregnant women in the beginning of the 1950's to alleviate nausea and insomnia. The result was that many of these women gave birth to children with horrible birth defects. The cause of all these problems was that the medicine was administered as a mixture of the two enantiomers. Whereas one of the enantiomers alleviated the nausea and insomnia, the other enantiomer prevented the normal grow and development of the fetus. Recently Softenon has been in the centre of attention again. It was found that in combination with the steroid dexamethason, Softenon has a decelerating effect on multiple myeloma (a type of bone marrow cancer).[3] This example shows the importance of enantiomerically pure compounds.[4]

1.2 Enantiomerically pure compounds

Enantiomerically pure compounds can be obtained in three different ways (Figure 1.3). The first route makes use of chiral compounds which are obtained from agriculture or via fermentation, the so called 'chiral pool'. These compounds can be used as obtained or modified without loss of the chiral information. The second route makes use of racemates *i.e.*, a 1:1 mixture of enantiomers. Separation of these racemates by resolution can be done in two ways.[5] Crystallization is still the most used method in industry to obtain enantiomerically pure compounds.[6] A racemate is derivatized with another chiral compound (auxiliary), so that diastereomers are formed, which can be separated by crystallization. Removal of the auxiliary gives the enantiomerically pure compound.

In a kinetic resolution, a racemate is modified by chemical or enzymatical conversion. In a kinetic resolution one of the enantiomers of the racemic mixture will be transformed into a product faster than the other. In an ideal case the reaction stops after 50% of conversion and only one of the enantiomers is completely converted and the other one did not react at all. In a dynamic kinetic resolution one of the enantiomers is transformed into the product, whereas the remaining enantiomer racemizes. This racemic mixture undergoes a resolution again until all the starting material has been consumed. This can lead in an optimal case to a yield of 100% and an enantioselectivity of 100%.

The third route makes use of prochiral substrates which can be transformed into enantiomerically pure compounds by an asymmetric synthetic modification. The asymmetric synthesis can be performed in different ways *i.e.,* using a chiral auxiliary[7] or applying catalysis.[8] In the case of a chiral auxiliary a chiral group is attached to the substrate. Introduction of an additional chiral centre will make the resulting product a diastereomer. In an ideal case the introduction of the additive stereogenic centre will be completely controlled by the chirality of the auxiliary and thus the reaction will be diastereoselective. Drawback of this method is that stoichiometric amounts of a chiral auxiliary have to be used, which have to be introduced and removed with two additional synthetic steps.

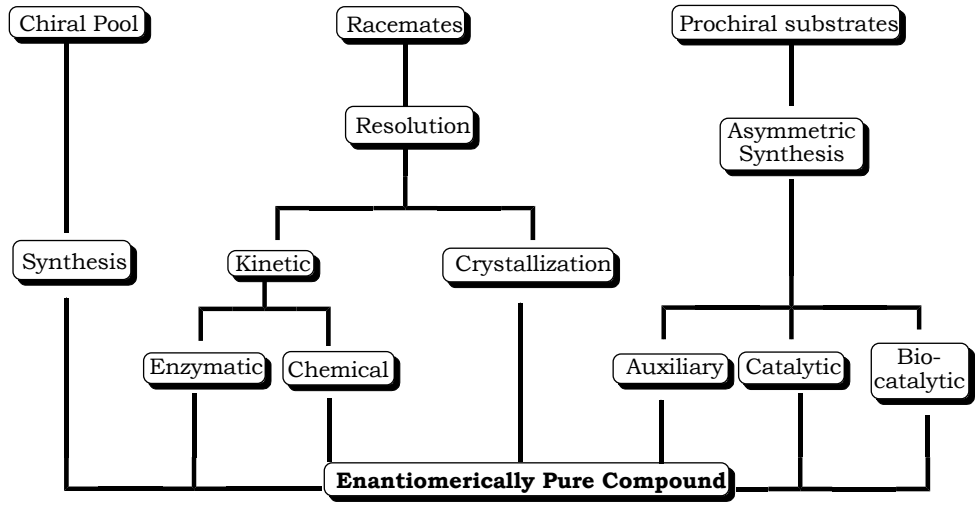


Figure 1.3: Routes to enantiomerically pure compounds.

A more elegant method is the application of catalysis, which is the main subject of this thesis. This method employs small amounts of a biological, *e.g.* antibodies or enzymes, or chemical catalysts to transform a prochiral substrate into large quantities of enantiomerically pure compounds. Biocatalysts are frequently highly specific for one substrate. In general, it is not possible to obtain both enantiomers of a product since usually only one of the enantiomers of a biocatalyst is available although recently directed enzyme evolution techniques have provided a solution to this problem.[9] On the other hand, chemical catalysts are commonly based on

(transition) metals modified with enantiomerically pure organic ligands, which makes it possible to obtain both enantiomers of the product by changing the configuration of the ligand. Asymmetric catalysis and more specific homogeneous asymmetric hydrogenations will be the central theme of this thesis. The next paragraphs will give an overview of these areas.

1.3 Asymmetric catalysis

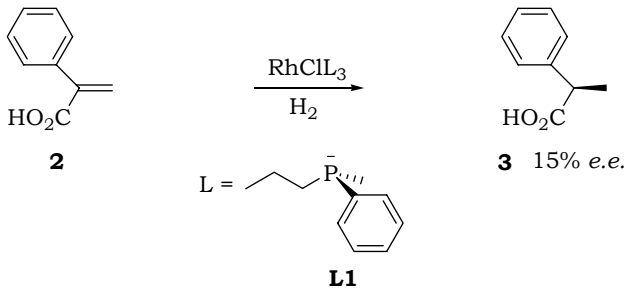
Although a broad range of organocatalysts have been developed in recent years,[10] (transition) metal catalysts are still the most abundantly used. The importance and elegance of homogeneous asymmetric catalysis was also recognized by the Nobel Prize Committee, who awarded the 2001 Noble Prize in chemistry to Knowles, Noyori and Sharpless for their pioneering work on asymmetric hydrogenation and oxidation reactions.[11] The field of (transition) metal-catalyzed asymmetric synthesis has developed tremendously and a wide variety of reactions have been developed employing a range of transition metals, *e.g.* Pd, Rh, Ru, Ir, Cu *etc.*[12] Homogeneous asymmetric hydrogenation is one of the most studied asymmetric catalysis reactions. An overview will be given in the next paragraph.

1.4 Homogeneous asymmetric hydrogenation

1.4.1 Asymmetric hydrogenations

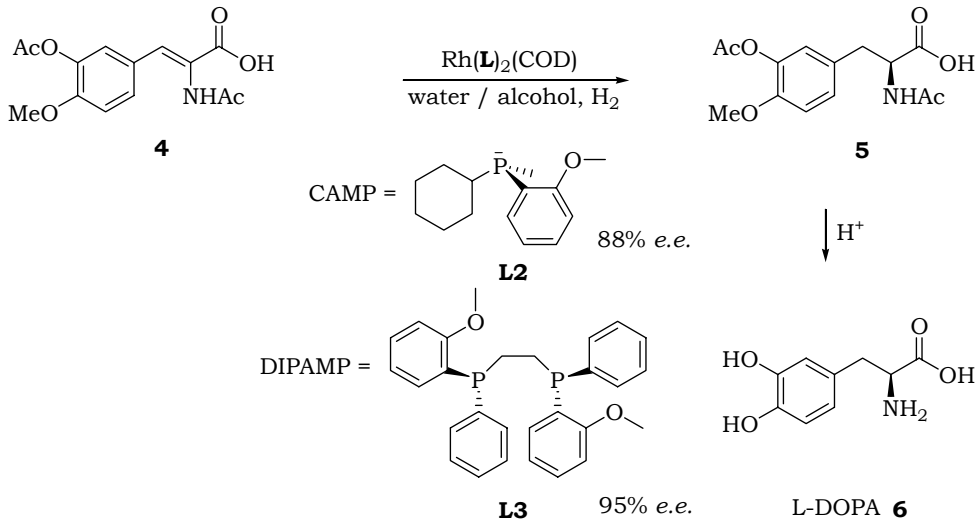
The field of homogeneous asymmetric catalytic hydrogenation has developed tremendously in the last 35 years. At the cradle of the development stand Knowles and Horner.[13] Their ground-breaking work was based on a combination of earlier developments of Wilkinson and Horner.[14] Wilkinson reported a soluble Rh-based hydrogenation catalyst for the hydrogenation of unhindered olefins *i.e.*, [$(PPh_3)_3RhCl$], whereas Horner reported the discovery of methods to prepare optically active phosphines. Initial experiments on α-phenylacrylic acid (**2**) with chiral methylpropylphenylphosphane (**L1**) gave an *e.e.* of 15% (Scheme 1.1).

Although the enantioselectivity was modest, a principle was proven and a new field of chemistry was born.

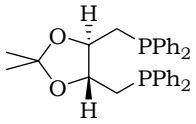


Scheme 1.1: Initial asymmetric hydrogenations by Knowles.

Further optimization of the phosphine revealed that CAMP (**L2**) was a good ligand in the hydrogenation of α-amino acid precursors (Scheme 1.2). This was applied in the industrial process of L-DOPA (**6**), an anti-Parkinson drug.



Scheme 1.2: Monsanto's L-DOPA process.

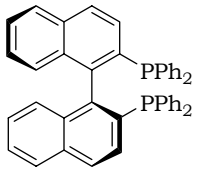


(*R,R*)-DIOP **L4**

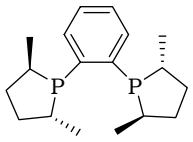
The initial hypothesis that a chiral phosphorus centre was necessary to obtain good enantioselectivities was proven to be incorrect. Kagan *et al.* developed a new ligand based on tartaric acid, which had the chirality shifted from the phosphorus to the backbone.[15] This new ligand, DIOP (**L4**), showed comparable results to CAMP (**L2**).

These results made Knowles and co-workers at Monsanto develop an improved version of their P-chiral ligands, *i.e.* DIPAMP (**L3**). This bidentate ligand showed even better results in the hydrogenation of the L-DOPA (**6**) precursor and the industrial process was converted to use it (Scheme 1.2).

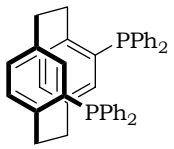
The shift of chirality from the phosphorus to the backbone made the synthesis of these ligands much easier and literally hundreds of ligands have been designed and tested in the following years.[16] In the next decades it was assumed that bidentate ligands are a *conditio sine qua non* to reach high selectivities. A number of successful ligands are depicted in Figure 1.4.



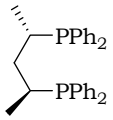
(*S*)-BINAP (**L5**)



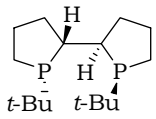
(*R,R*)-Me-DuPhos (**L6**)



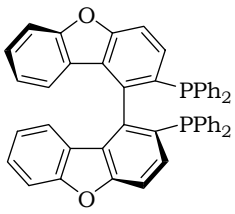
(*S*)-[2,2]-PhanePhos (**L7**)



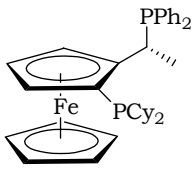
(*S,S*)-BDPP (**L8**)



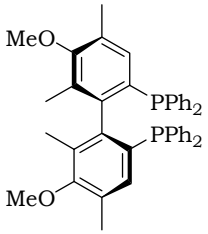
(1*S,1S',2R,2R*')-Me-PennPhos (**L9**)



(*S*)-BIFAP (**L10**)



(*R*)-(*S*)-JosiPhos (**L11**)



(*S*)-BIMOP (**L12**)

Figure 1.4: Successful bidentate ligands.[17]

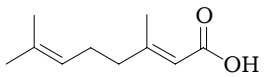
1.5 Monodentate ligands in asymmetric hydrogenations

The widely held view that bidentate ligands are essential for high enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation was turned down in 2000. Three groups reported, independently, the use of monodentate phosphonites[18], phosphoramidites[19] and phosphites[20] in the hydrogenations of several benchmark substrates. Since then numerous reports have appeared on the use of monodentate ligands in rhodium-catalyzed hydrogenations.[21]

1.5.1 Structure of monodentate ligands

1.5.1.1 P-chiral[22] monodentate ligands

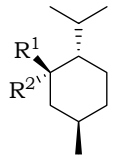
The initially developed monodentate ligands were P-chiral.[23] The results of these ligands in the rhodium-catalyzed hydrogenation of dehydroamino acids varied from almost non selective up to 90% *e.e.* for CAMP (**L2**).[11] Often a tedious synthesis is needed to obtain these ligands in enantiomerically pure form. This, in combination with the fact that the chirality could be shifted to the backbone (see §1.4.1) and the paradigm that ligands should be bidentate in nature, made that only a limited number of monodentate P-chiral ligands have been reported in literature. A few examples are given in Figure 1.5.



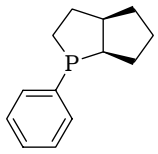
7

Ligands **13**, based on a menthyl backbone, were tested in the chemo- and enantioselective hydrogenation of (*E*)-3,7-dimethyl-2,6-dienoic acid (geranic acid) (**7**).[24] The *e.e.'s* were modest, with a maximum of 45% for **L13a**. On the other hand, the chemoselectivity was excellent. The only product observed was the product with the double bond next to carboxylic acid moiety reduced. Monodentate phosphines **L14** and **L15** led to modest enantioselectivities in the hydrogenation of *N*-acetyl dehydrophenylalanine (**8**), 62% and 10%, respectively. These two ligands were more successful in palladium-catalyzed allylic substitution reactions, where up to 95% *e.e.* has been obtained.[25] Reetz and co-workers recently introduced ligands **L16**-**L19**, based on a BINOL backbone bearing a single *ortho*-substituent.[26] The monodentate phosphoramidite and

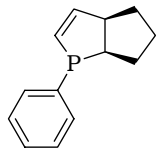
phosphite ligands were formed as diastereomer mixtures and had to be separated by preparative HPLC.[27] Many of these ligands induced excellent *e.e.'s* (> 95%) in the hydrogenation of dimethyl itaconate (**19**) and *N*-acetyl dehydroalanine methyl ester, both in diastereomerically pure form as in mixtures of diastereoisomers. Secondary phosphine oxide ligands **L20** proved to be versatile ligands in rhodium- and iridium-catalyzed hydrogenations of a broad range of substrates.[28] Enantioselectivities up to 85% were obtained in the hydrogenations of for example imines and β-branched dehydroamino acids (§1.5.3.1).



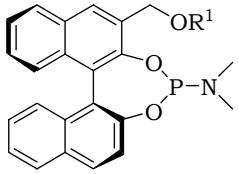
L13a: R^1 = (*S*)-PPh, Me R^2 = H
L13b: R^1 = (*R*)-PPh, Me R^2 = H
L13c: R^1 = H, R^2 = (*S*)-PPh, Me
L13d: R^1 = H, R^2 = (*R*)-PPh, Me



L14

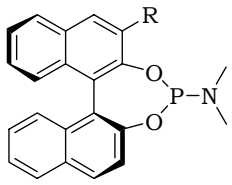


L15



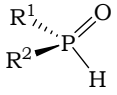
L16

L16a: R = C(O)Ph
L16b: R = CH_3
L16c: R = CH_2Ph



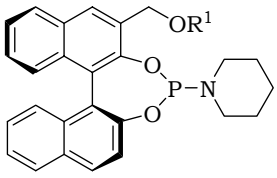
L17

L17a: R = CH_3
L17b: R = Ph
L17c: R = SPh
L17d: R = $SiMe_3$
L17e: R = $SiPh_3$



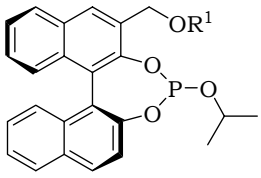
L20

L20a: R^1 = *t*-Bu, R^2 = Ph
L20b: R^1 = *i*-Pr, R^2 = Ph
L20c: R^1 = *t*-Bu, R^2 = 2-naphthyl
L20d: R^1 = *t*-Bu, R^2 = 2-MeO-Ph
L20e: R^1 = *t*-Bu, R^2 = 3,5-di-Me-Ph
L20f: R^1 = *t*-Bu, R^2 = 2,4,6-tri-Me-Ph
L20g: R^1 = Ph, R^2 = 2-naphthyl



L18

L18a: R^1 = C(O)Ph
L18b: R^1 = CH_3
L18c: R^1 = CH_2Ph

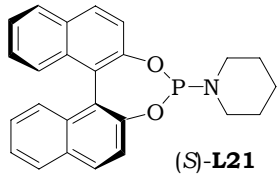


L19

L19: R^1 = CH_2Ph

Figure 1.5: P-chiral ligands.

1.5.1.2 Non P-chiral monodentate ligands



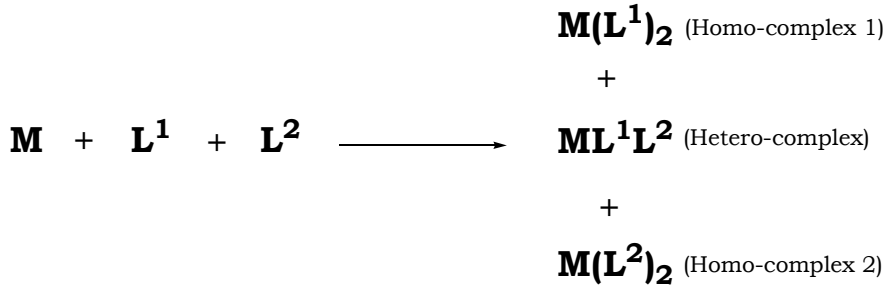
(*S*)-**L21**

The most abundant monodentate ligands are non P-chiral in nature. With the exception of a few monodentate phosphines, most of the monodentate non P-chiral ligands are based on chiral diols.[21] Ligands based on BINOL are easy to synthesize and have been highly successful (see also chapter 2). Furthermore, BINOL is commercially available at relative low cost. One of the most successful BINOL-based ligands is monodentate phosphoramidite **L21**. This ligand showed excellent results in the Rh-catalyzed hydrogenation of a wide variety of substrates, such as *a*-dehydroamino acids, enamides, itaconic acids, enol esters and enol carbamates.[47a, 52] A drawback of BINOL is the rather difficult structural modification. This is one of the reasons why a wide variety of other backbones have been used in the recent years, such as biphenols,[29] spiro based diols[30], BICOL[31] (see chapter 3) and catechol[47] (see chapter 2). Most of these ligands showed excellent results in the hydrogenation of a variety of substrates. As was shown by Reetz *et al.* the chirality of the hydrogenation product is in most cases dictated by the chiral backbone.[20] The chirality of the other moiety is not important and as was shown before, one of the best ligands reported so far is bearing an achiral piperidine moiety. The remarkable beneficial effect of the piperidine moiety was also found in the other ligands. In the Rh-catalyzed hydrogenation of *a,ß*-unsaturated acids and *N*-acyl *ß*[2]-dehydroamino acids mixed ligands systems of chiral phosphoramidites and achiral phosphines were used (see chapters 5 and 6). The chiral phosphoramidite is based on a substituted BINOL and a piperidine moiety.

1.5.2 Mixtures of monodentate ligands

Reetz[32] and Feringa / Minnaard / De Vries[33] independently showed that the catalytically active species in the rhodium-catalyzed hydrogenation with monodentate ligands bears two of these monodentate ligands. This feature gives monodentate ligands the unique possibility to use two *different* monodentate ligands, instead of one bidentate ligand, for the formation of the chiral complex. By mixing a metal precursor with two equivalents of two *different* monodentate ligands, three different complexes

can be formed *i.e.*, two homo-complexes and a hetero-complex (Scheme 1.3). [34]



Scheme 1.3: The monodentate ligand combination approach.

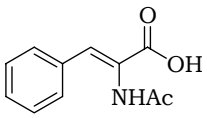
If the hetero-complex is more active and induces a higher enantioselectivity than the two homo-complexes, the *e.e.* of the product will be higher than up on use of the homo-complexes. A first attempt to use this approach was made by Chen and Xiao.[35] Up to 75% *e.e.* was obtained in the rhodium-catalyzed hydrogenation of dimethyl itaconate (**19**) applying diastereomeric mixtures of biphenyl ligands. Unfortunately, formation of the hetero-complex in these mixtures was not observed by ^{31}P-NMR. Combining diastereomeric mixtures gave the average of the two diastereomeric mixture independently, which indicates that also in this case no hetero-complex formation takes place.

The first successful experiments with combinations of monodentate ligands were reported by Reetz[36] and Feringa / De Vries / Minnaard.[37] Combinations of chiral phosphites and phosphonites or phosphoramidites led in some cases to higher *e.e.'s* in the rhodium-catalyzed hydrogenation of dehydroamino acids or enamides than their corresponding homo-combinations. This new strategy has been employed, not only in rhodium-catalyzed hydrogenation,[38] but also in rhodium-catalyzed additions of boronic acids[39] and rhodium-catalyzed hydroformylations.[40] In some cases, mixtures of chiral and *achiral* monodentate ligands gave significant higher *e.e.'s* than their corresponding homo-complexes (see chapter 5).[38f] An interesting effect was reported by Reetz and Mehler,[38a] where a combination of a chiral and an achiral ligand reversed the absolute configuration of the product compared to the corresponding homo-complex of the chiral monodentate ligand. The concept of improved

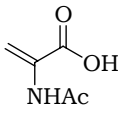
enantioselectivities by nonchiral additives or by achiral and meso ligands has precedent and has been recently reviewed.[41]

1.5.3 Substrates for Rh-catalyzed hydrogenation with monodentate ligands

1.5.3.1 N-acyl α-dehydroamino acids and esters

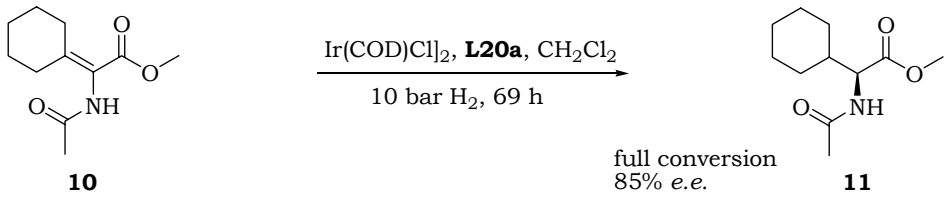


N-acyl *α*-dehydro-phenylalanine (**8**)



N-acyl *α*-dehydro-alanine (**9**)

The most studied class of substrates in the rhodium-catalyzed asymmetric hydrogenation is the *N*-acyl α-dehydroamino acids and esters. Hydrogenation of these molecules leads to the synthesis of α-amino acids, which are interesting molecules from an industrial point of view. A wide variety of newly developed chiral monodentate phosphites, phosphoramidites and phosphonites have proven to be excellent ligands in the hydrogenation of **8** and **9**.[21] A more difficult class of substrates is those with a tetra-substituted double bond. Only one example is known in the literature, in which a secondary phosphine oxide has been used in the hydrogenation of **10** in an Ir-catalyzed reaction.[28a] A good enantioselectivity was obtained, however with a low reaction rate (Scheme 1.4).



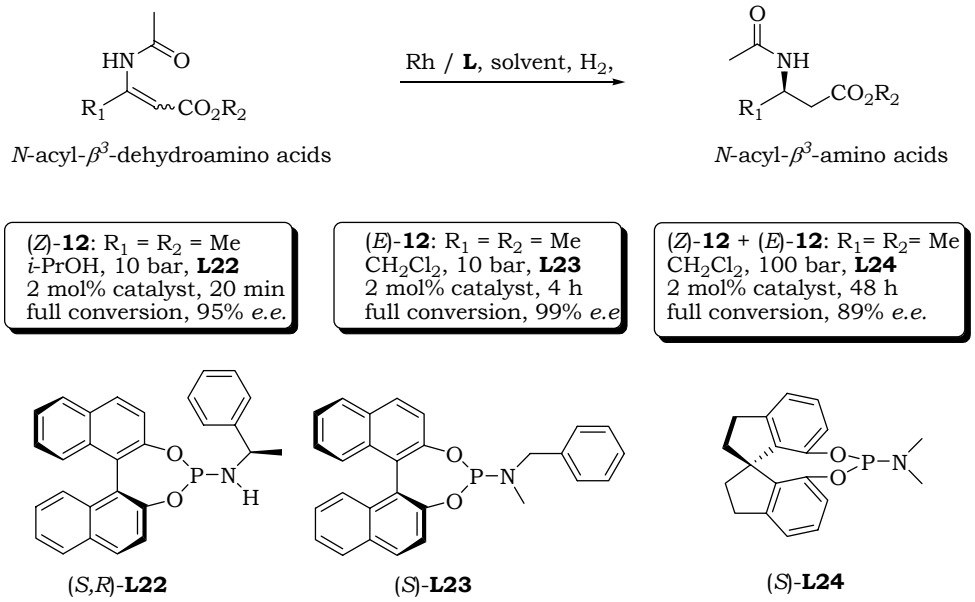
10 **11**

Scheme 1.4: Ir-catalyzed of substrate **10**.

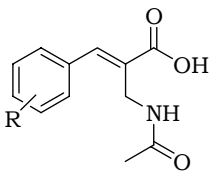
1.5.3.2 N-acyl β-dehydroamino acids

Less studied, but certainly not less interesting, is the hydrogenation of *N*-acyl *β*^{3}-dehydroamino acids. A limited number of reports have been published on the Rh-catalyzed asymmetric hydrogenation with

monodentate ligands of these substrates. Although monodentate phosphites gave good results,[42] so far, monodentate phosphoramidites gave the better results in the hydrogenation of *N*-acyl *β*^{3}-dehydroamino acids (Scheme 1.5).[43] Phosphoramidites **L22** and **L23** gave excellent results in the hydrogenation of *N*-acyl *β*^{3}-dehydroamino acids with respectively an *E*- and *Z*-configuration.[43a] On the other hand, the Rh-catalyst based on Zhou's SIPHOS (**L24**) is able to hydrogenate mixtures of *Z*- and *E*-isomers in good yields. This saves a tedious separation of the isomers, since *N*-acyl *β*^{3}-dehydroamino acids are normally obtained as mixtures of *Z*- and *E*-isomers.



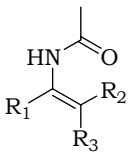
Scheme 1.5: Rh-catalyzed hydrogenation of *N*-acyl *β*^{3}-dehydroamino acids with monodentate phosphoramidites.


N-acyl *β*^{2}-dehydro-phenylalanine

Only a few reports have been published on the hydrogenation of *N*-acyl *β*^{2}-dehydroamino acids. Bidentate phosphine ligands have not been very successful so far and modest enantioselectivities have been obtained (see chapter 6).[44] A new catalytic system, based on a mixture of an *achiral* phosphine and a chiral monodentate phosphoramidite, has been

developed. This catalytic system gave good enantioselectivities (> 90%) in a series of substituted (*E*)-*N*-acyl β^2-dehydrophenylalanine (see chapter 6).

1.5.3.3 N-acyl enamides, enol esters and enol carbamates



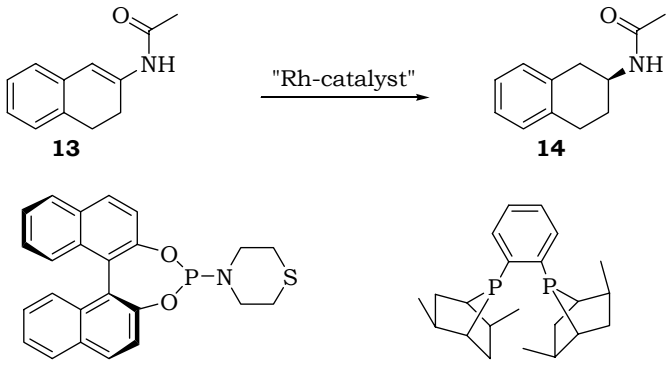
N-acyl enamide

R_1 = alkyl, or aryl,
R_2, R_3 = alkyl

Enantiomerically pure amines, which are interesting building blocks for drug design and discovery, can be obtained by rhodium-catalyzed hydrogenation of *N*-acyl enamides with subsequent hydrolysis of the amide bond. The synthesis of these substrates is tedious (see chapter 2), which might be the reason why this class of substrates is less studied compared to the class of α-dehydroamino acids.

Nevertheless, a number of monodentate phosphoramidites and phosphites are capable of hydrogenating a range of *N*-acyl enamides. Enantioselectivities up to 99% have been achieved in this class of substrates (see chapter 2).[21] Two interesting and still challenging substrates, are **13** and **15**. Limited reports have been published regarding these substrates, with in general disappointing results. Enantiomerically pure **14**, or substituted derivatives thereof, are present in several biological active compounds.[45]

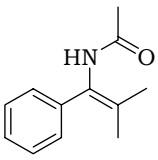
Reasonable results for the rhodium-catalyzed hydrogenation of **13** have been obtained with a bidentate ligand, PennPhos (**L26**) (71% *e.e.*), developed by Zhang and co-workers (Scheme 1.6).[46] So far, monodentate ligands have not been very successful in the hydrogenation of **13**.[47] The best result published is with BINOL-based phosphoramidite **L25**, which in the hydrogenation of **13** results in 34% *e.e.* with full conversion at 25 bar H_2 at room temperature for 8h (Scheme 1.6). However, the best results obtained for the hydrogenation of **13** were published by Bruneau and co-workers. They used a Ru / BINAP catalyst, which gave up to 90% *e.e.* Just recently, Jiang *et al.* published a remarkably breakthrough in the rhodium-catalyzed hydrogenation of **13**. They were able to hydrogenate **13** with 94% *e.e.* and full conversion employing a supramolecular catalyst, which was based on a bidentate ligand containing a BINOL moiety and a porphyrine moiety.[48]



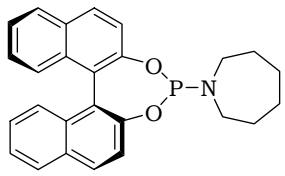
(*S*)-**L25**: 34% *e.e.* (*R,S,R,S*)-PennPhos (**L26**): 71% *e.e.*

Scheme 1.6: Rhodium-catalyzed hydrogenation of enamide **13**.

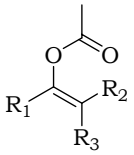
The hydrogenation of tetrasubstituted enamides with monodentate ligands is still challenging. As was observed in the hydrogenation of α-dehydroamino acids with tetrasubstituted double bonds, in general, low conversions and low enantioselectivities are obtained for the hydrogenation of **15** with monodentate ligands.[47a,b,49] Although full conversion, only 27% *e.e.* has been achieved with **L27**.[50] More successful were the bidentate phosphines BisP* and MiniPhos, developed by Imamoto and co-workers.[51] Catalysts based on these ligands were able to hydrogenate **15** with 99% and 98% *e.e.*, respectively.



15

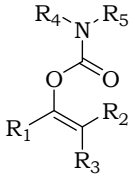


(*S*)-**L27**: 27% *e.e.*



Enol acetates

R_1 = alkyl, or aryl,
R_2, R_3 = alkyl, H

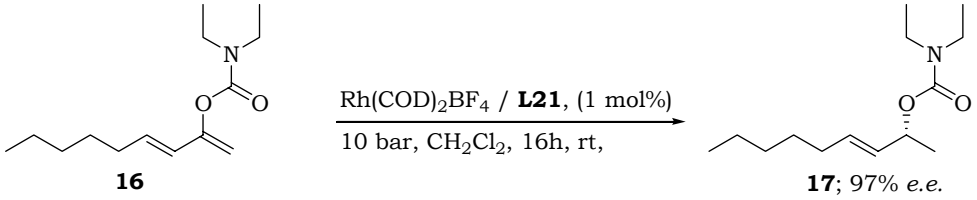


Enol carbamates

R_1 = alkyl, or aryl,
R_2, R_3 = alkyl, H
R_4, R_5 = alkyl

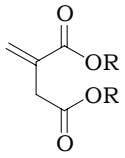
An alternative for the Ru-catalyzed hydrogenation of ketones to alcohols is the Rh-catalyzed hydrogenation of enol acetates or enol carbamates to protected alcohols. In a recent published study, a series of aromatic enol acetates, alkyl and aromatic enol carbamates could be hydrogenation with *e.e.'s* up to 98% with PipPhos (**L21**).[52] Remarkable was the selective hydrogenation of **16**, to the

corresponding allyl carbamate. Allyl carbamate **17** was obtained with an enantioselectivity of 97% as the sole product (Scheme 1.7).



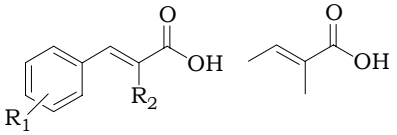
Scheme 1.7: Selective hydrogenation of enol carbamate **16**.[52]

1.5.3.4 Unsaturated acids and esters



18: R = H
19: R = Me

The hydrogenation of itaconic acid (**18**) and its dimethyl ester **19** is considered, next to the hydrogenation of *N*-acyl α-dehydroamino acids and esters, as a benchmark reaction. In the last 6 years a great number of monodentate ligands have been reported which can be used in the hydrogenation of these substrates in excellent enantioselectivities with high turn over frequencies.[21]



α-substituted cinnamic acids

Tiglic acid (**20**)

Less studied is the hydrogenation of other unsaturated acids, such as α-substituted cinnamic acids or tiglic acid (**20**). This is not surprising, since it is known that a secondary coordination of a suitable positioned carbonyl plays an important role in the hydrogenation (see also §1.5.4).[53] Only a few reports have been published on the Rh-catalyzed hydrogenation of α-substituted cinnamic acids and **20** (see chapter 5).[54] The best results obtained are with a catalyst based on a mixed ligand system of an *achiral* phosphine and a *chiral* monodentate phosphoramidite.[38e] The results are described in chapter 5. Enantioselectivities up to 99% have been achieved with this system.

1.5.4 Rh-substrate complexes in asymmetric hydrogenations

As was mentioned before, the possibility of a secondary coordination by a carbonyl functionality of a substrate is believed to be essential for high enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation.[53] The most relevant mechanism for the Rh-catalyzed hydrogenation is the unsaturated mechanism proposed by Halpern (Figure 1.6).[56,55]

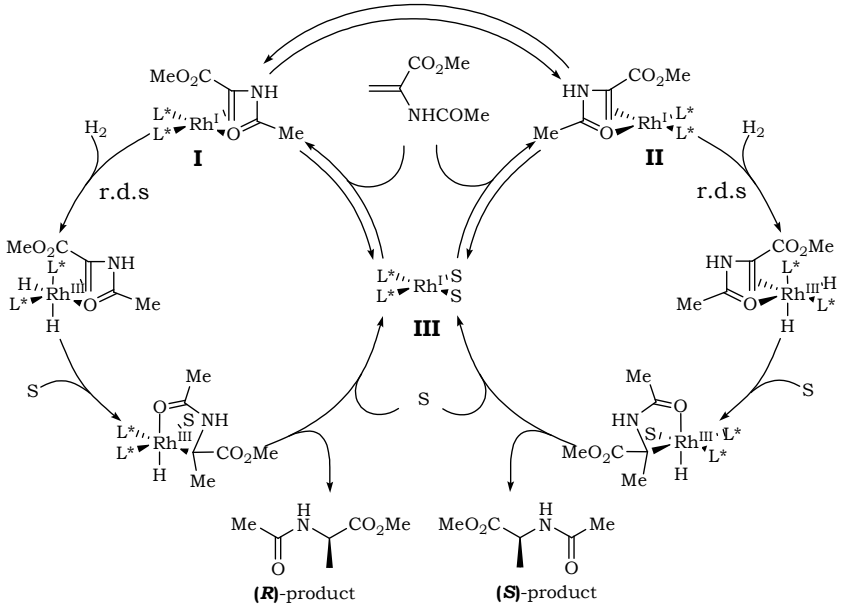


Figure 1.6: Simplified representation of Halpern-mechanism (charges not indicated).[56]

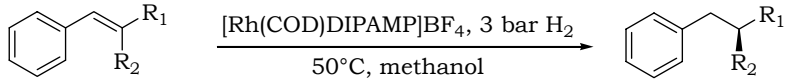
The initial step is the reversible coordination of the substrate to a cationic catalyst precursor (**III**), forming the diastereomeric complexes **I** and **II**. The two diastereomeric complexes are in equilibrium with each other. Whereas one of these complexes gives the product with a *R*-configuration, the other complex gives the product with a *S*-configuration. The formation of these complexes is followed by oxidative addition of H_2 (= r.d.s.)† and subsequently migratory insertion of the olefin into the Rh-H

† r.d.s. = rate determining step

bond. In the last step the product is released by reductive elimination and the original catalytic precursor (**III**) is recovered.

The secondary coordination via the carbonyl reduces the rotational freedom of the substrate around the rhodium centre. The importance of this secondary coordination was shown by Vineyard *et al.,* in a systematic study of substituents around the double bond (Table 1.1).[53]

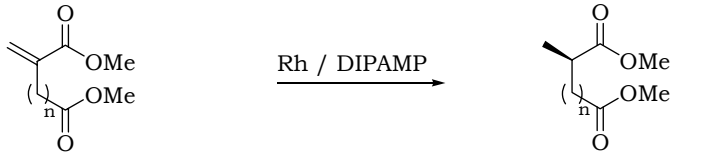
Table 1.1: Structure effect of substrate on enantioselectivity.[53]



Entry	R_1	R_2	*E.e. of product (%)*
1	COOH	NHAc	95
2	COOMe	NHAc	97
3	$C(O)NH_2$	NHAc	94
4	CN	NHC(O)Ph	88
5	Ph	NHAc	65
6	Me	NHAc	51
7	COOH	OC(O)Me	90
8	Me	COOH	<1

As can been seen from these data, the nature of the R_1 substituent has not a major influence on the enantioselectivity of the products. Carboxylic acids, esters, amides and cyano groups give good enantioselectivities (entries 1-4). The *e.e.'s* drop when an alkyl group is introduced in the R_1 position (entries 5 and 6). Introduction of an enol ester at R_2 gave the hydrogenated product with 90% *e.e.* This suggests that the nature of the carbonyl is of less importance. However, when R_2 is changed from an amide to a carboxylic acid, the product was obtained in racemic form (entry 8). This, on the other hand, suggests that not only the presence of a carbonyl is important, but also the position of the carbonyl, *i.e.* the size of the formed chelate. This was shown by Vineyard and co-workers in the hydrogenation of itaconic acid dimethyl ester (**19**) and its analogue α-methyleneglutaric acid dimethyl ester (**21**) (Scheme 1.8). Itaconic acid could be hydrogenated with an *e.e.* of 88%, whereas introduction of an extra CH_2-group, and thus increasing the chelate ring of the substrate,

reduced the enantioselectivity dramatically. This catalytic system, based on Rh and DIPAMP (**L3**) favors the formation of 6 membered chelates of the substrate, whereas other catalytic systems have proven to be able to hydrogenate substrates which form 5- or 7-membered chelate rings with the substrate. In general, bisphosphine ligands with a large bite angle, such as DIOP (**L4**) (96°), form strong complexes with substrates that form a small chelate ring with the substrate, whereas bisphosphines with a small bite angle, such as DIPAMP (**L3**) (82°), do not form characterizable complexes with these kind of substrates.[57b]



19: n = 1
21: n = 2

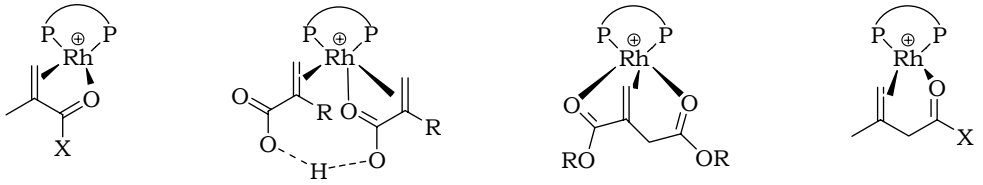
22: n = 1, 88% *e.e.*
23: n = 2, 3%, *e.e.*

Scheme 1.8: Rh-catalyzed hydrogenation of **19** and **21**.

Although to a lesser extent, the electronic properties of the carbonyl are also important. For example, the hydrogenations of unsaturated carboxylic acids are in general slower than the hydrogenations of enamides. This is attributed to the fact that carboxylic acids have a weaker coordination with Rh than amides. A similar effect was observed in our system; The hydrogenation of α-substituted cinnamic acids could be performed with high enantioselectivities, while the corresponding methyl ester could not be hydrogenated (see chapter 5). This might be also the reason why the hydrogenation of this class of substrates is less studied then other classes. The hydrogenation of unsaturated carboxylic acids demands a finely tuned catalytic system (see chapter 5).

Whereas, amides form well-defined Rh/substrate complexes, carboxylic acids can form different types of Rh/substrate complexes as was shown by Brown *et al.*[57] In general, four different kinds of Rh-complexes can be formed by carboxylic acids and carboxamides, depending on the ligand, substrate and base (Figure 1.7).

As mentioned before, the structure of the ligand is of importance for the formation of the Rh-complexes. With seven-membered-ring ligand chelates, *i.e.* DIOP, formation of complex **A** is favored with sufficiently bulky acids, such as atropic or cinnamic acids. The formation takes places, preferentially in the presence of base. Unhindered acids, such as propenoic and 2-methyl propenoic acid also form complexes with structure **A** in the presence of base. However, in the absence of base, complexes with the structure of **B** are preferred, with a 2:1 stoichiometry of acid : Rh. The formation of **B** is relatively slow. A range of complexes are formed with itaconic acids and its esters with a range of Rh-DIPAMP complexes. Complexes **A**, **C**, and **D** have been observed. The authors conclude that there is little resemblance between the structure of the complexes, diastereomer ratios formed and the optimal enantioselectivity.[58] It should be noted that, highest reactivities have been observed for complexes having a five-membered-ring ligand chelate and a bidentate substrate.



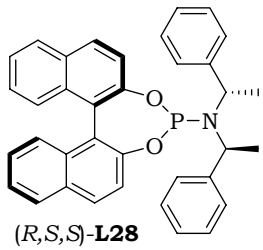
A X = O^-, NR_2 **B** R = H, Me **C** X = OH, OMe **D** R = H, Me

Figure 1.7: Types of Rh / bisphosphine complexes formed with carboxylic acids and carboxamides.

1.6 Monodentate phosphoramidites in other transition metal catalyzed reactions

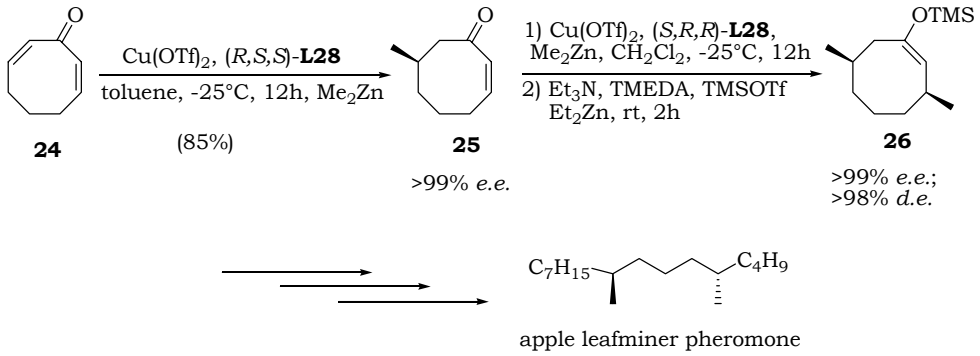
In addition to asymmetric hydrogenations, chiral monodentate ligands have proven to be very effective in the introduction of enantioselectivity in a broad range of other transition metal catalyzed reactions.[59] In this paragraph an overview will be given of monodentate phosphoramidites in transition metal catalyzed reactions in 2004 and 2005.

1.6.1 Conjugate additions



(*R,S,S*)-**L28**

The first successful application of chiral monodentate phosphoramidites has been in the Cu-catalyzed conjugate additions of dialkylzinc derivatives to *a,ß*-unsaturated ketones.[60] The most successful ligand is **L28**, developed by Feringa and co-workers. In addition to enones,[61] the conjugate addition to a variety of other unsaturated substrates has been reported in the last two years, *i.e.* lactams,[62] malonates,[63] epoxides,[64] imines[65] and nitro olefins.[66] A variety of other ligands have proven to be successful as well. In general, those ligands are derivatives of **L28**. Interesting is also that this chemistry has been applied as key-steps in syntheses of bio-active compounds. [61a,c,g] [66a,c] An attractive example is the synthesis of apple leafminer pheromones (Scheme 1.9).[61g]

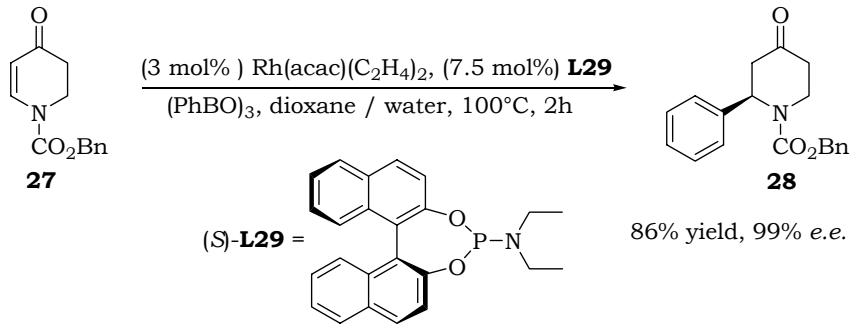


Scheme 1.9: Synthesis of apple leafminer pheromone.[61g]

The key-step in this synthesis is a Cu-catalyzed double conjugated 1,4-addition of dimethylzinc to cycloocta-2,7-dienone (**24**). Van Summeren *et al.* were able to synthesize all 4 diastereoisomers in >99% *e.e.* and with *d.e.'s* of over 98%, by choosing the appropriate ligand in each step. The product of the second 1,4-addition was isolated as its TMS-enol ether, since quenching would afford the nonchiral *meso*-compound.

Phosphoramidites have been applied, not only in the Cu-catalyzed conjugate addition of dialkylzinc reagents, but also in the Rh-catalyzed addition of boron compounds.[67] Like in the Cu-catalyzed 1,4-additions, excellent enantioselectivities (99%) have been obtained in Rh-catalyzed

additions. A representative example is depicted in Scheme 1.10. A phenyl group could be introduced into a pyridone moiety with high enantioselectivities and good yields. The products are interesting intermediates for natural compounds or drug candidates, since the piperidine ring system is frequently encountered in these systems.



Scheme 1.10: Rh-catalyzed conjugate addition of phenylboroxine.[67d]

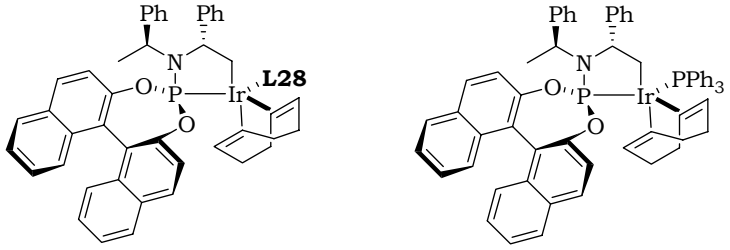
1.6.2 Allylic substitutions

After the initial reports by Hartwig and co-workers,[68] a number of reports on the use of phosphoramidites in the Ir-catalyzed allylic amination or etherfication have been published.[69] Helmchen and co-workers applied this method in the synthesis of a variety of heterocycles. Excellent results have been obtained in the synthesis of substituted pyrolidines and pyridines with enantioselectivities of >99%. Again, the most successful ligand was **L28** or derivatives thereof.

The Ir-catalyzed alkylation with monodentate phosphoramidites has been reported before, but in contrast to the amination and etherification, the results were not very satisfactory.[70] Enantioselectivities were low, regioselectivities covered a range between 30:70 to 91:9 for, respectively, the branched and linear products and reaction times were long. From earlier work it was known that an initial active catalyst was formed, when a base was added to a mixture of [{Ir(COD)Cl}$_2$] and **L28**, which lost reactivity after several hours. [71]

The inactive catalyst was identified as **29** (Figure 1.8). The base is necessary for the CH-activation, which forms the active complex,

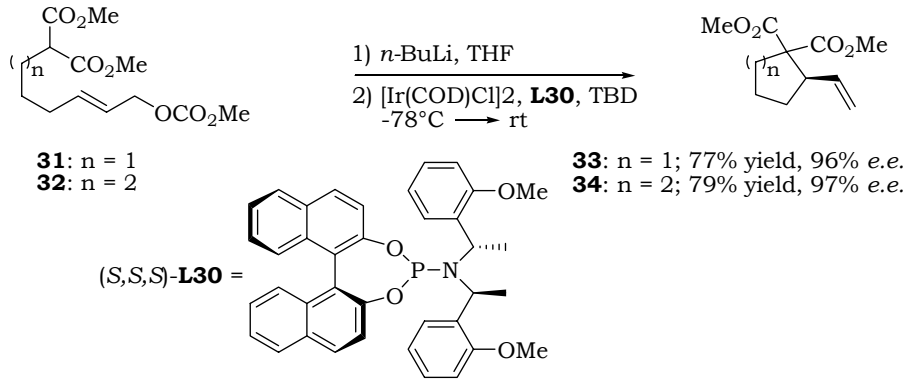
coordination of a second ligand satisfies the coordination places and deactivates the catalyst. A substantial improvement was reported by Lipowski *et al.*[72] Complex **30** (Figure 1.8) was obtained after adding TBD‡ to a 1:1:1 mixture of [{Ir(COD)Cl}$_2$], **L28** and PPh_3.



29 **30**

Figure 1.8: Complexes **29** and **30**.

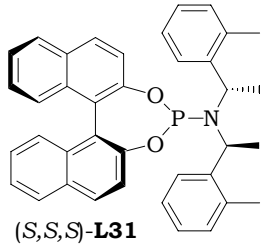
Complex **30** showed low catalytic activity,[73] but an active catalyst was obtained after addition of CuI.[74] The CuI acts as a scavenger by selective removal of the PPh_3 from the complex. Removal of the PPh_3 creates a free coordination place for the substrate. Streiff *et al.* applied this approach of catalyst activation in the synthesis of carbocycles (Scheme 1.11).[75]



Scheme 1.11: Synthesis of **33** and **34** by intramolecular Ir-catalyzed allylic alkylation.[75]

‡ TBD = 1,5,7-triazabicyclo[4.4.0]undec-5-ene

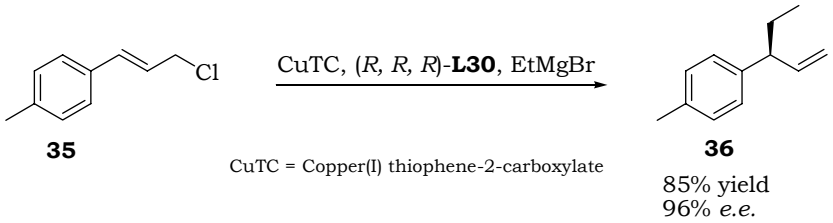
Furthermore, Alexakis and co-workers reported the use of **L30** in the Ir-catalyzed alkylation of series of benchmark substrates, with high enantioselectivities and good branched : linear regioselectivities.[76]



(*S,S,S*)-**L31**

In a comparative study of different phosphoramidites, it was shown that slight differences in the substitution pattern of the aryl group of the amine moiety of **L28** strongly influences the activity of the ligand, whereas the *e.e.*'s of the different ligands were in a comparable range.[76] The highest reactivity and enantioselectivities were observed for **L31**.

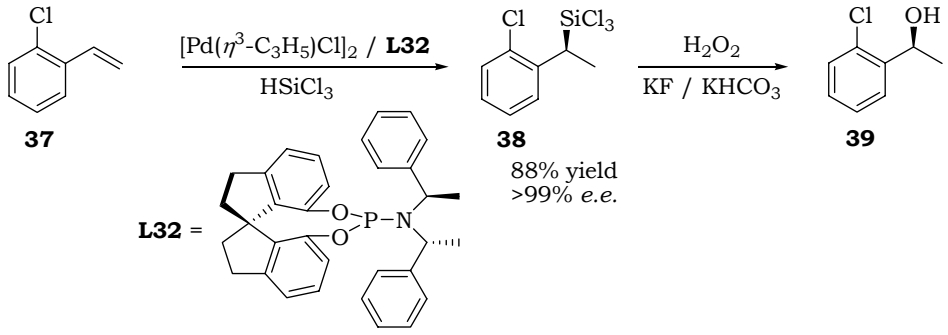
A few reports have also been published on Cu-catalyzed[77] and Pd-catalyzed[78] allylic substitutions with phosphoramidites. Whereas the results in Pd-catalyzed allylic substitution were modest, excellent results have been obtained in the Cu-catalyzed allylic alkylation with Grignard reagents (Scheme 1.12). For example, **36** could be isolated in 85% yield with 99 : 1 ratio of branched / linear product and an *e.e.* of 96%.



Scheme 1.12: Cu-catalyzed allylic substitution with Grignard reagents.[77a]

1.6.3 Hydrosilylations

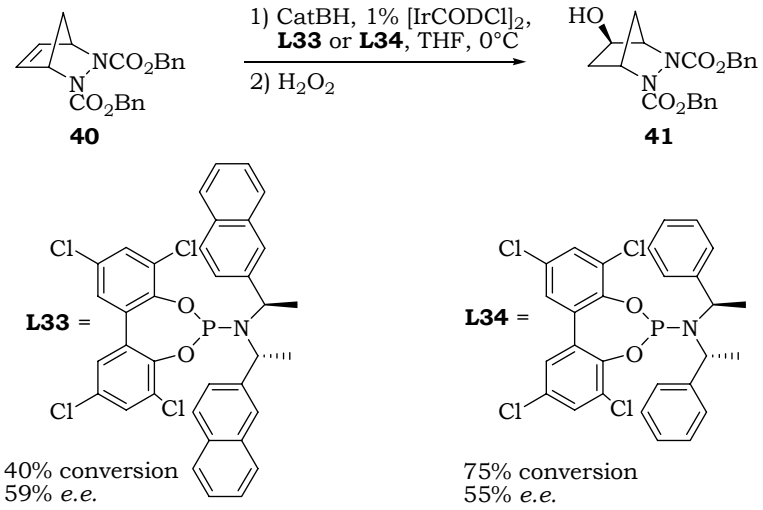
Zhou and co-workers reported a series of spiro phosphoramidites which have been used in different transition metal catalyzed reactions, *e.g.* Pd-catalyzed hydrosilylation,[79] Pd-catalyzed hydrovinylation (§1.6.6), Rh-catalyzed asymmetric Pauson-Khand (§1.6.9), Cu-catalyzed ring opening (§1.6.7) and Rh-catalyzed asymmetric hydrogenations (§1.5.1.2). In the Pd-catalyzed hydrosilylation of styrene derivatives enantioselectivities up to 99% have been achieved. Oxidation of the obtained silanes afforded the corresponding chiral alcohols (Scheme 1.13).



Scheme 1.13: Pd-catalyzed hydrosilylation with spiro phosphoramidites.[79]

1.6.4 Hydroborations

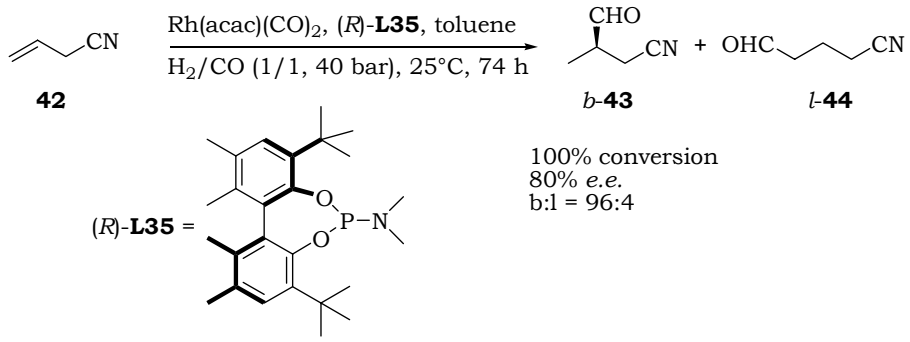
Biphenol–based ligands **L33** and **L34** showed reasonable results in the hydroboration of *meso*-bicyclic hydrazines (**40**) (Scheme 1.14).[80] The chloride substituents proved to be important, since phosphoramidites with other substituents on these positions gave lower selectivities. BINOL-based phosphoramidites gave rather disappointing results with a maximum of 18% *e.e.*



Scheme 1.14: Ir-catalyzed hydroboration with biphenol-based phosphoramidites.[80]

1.6.5 Hydroformylations

Biphenol-based phosphoramidites have proven to be also versatile ligands for the Rh-catalyzed hydroformylation.[61h] Good enantioselectivities and very good regioselectivities could be obtained in the hydroformylation of allyl cyanide (**42**) (Scheme 1.15). **L35** gave up to 80% *e.e.* with a b/l (= branched / linear) ratio of 96:4 at a temperature of 25°C. A drawback was the long reaction time of 74 h for full conversion. Increasing the temperature to 50°C gave full conversion in 5 h. In the latter case a slight drop of *e.e.* was observed (76%) with more unfavorable b/l ratio (92:8). Compound *b*-**43** is particularly interesting, since it is an intermediate for TAK-637, a drug candidate for treatment of urinary continence.

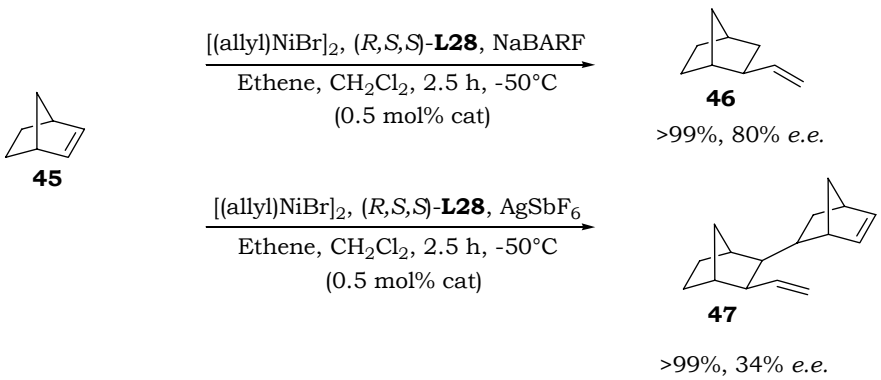


Scheme 1.15: Rh-catalyzed hydroformylation with biphenol-based phosphoramidites.[61h]

1.6.6 Hydrovinylations

As mentioned before, the spiro phosphoramidites developed by Zhou and co-workers have also been tested in the Pd-catalyzed hydrovinylation of styrene derivatives.[81] Up to 92% *e.e.* has been obtained although the selectivity towards the desired product was only 10%. In the cases were the selectivity towards the product was better (up to 85%) the enantioselectivity dropped (55%).

More interesting are the results obtained by Park *et al.*[82] in the Ni-catalyzed hydrovinylation of norborene (**45**). BINOL-based ligand (*R,S,S*)-**L28** gave 80% *e.e.* with a selectivity of 99% when NaBARF[§] was used as an additive. Changing the additive to $AgSbF_6$ gave the 2:1 adduct (**46**) selectively but with only 34% *e.e.* Perhaps more striking is the effect of the ligand. When the diastereomer (*R,R,R*)-**L28** was used with NaBARF as an additive, hardly any conversion was obtained (Scheme 1.16).



Scheme 1.16: Asymmetric Ni-catalyzed hydrovinylation of norborene with phosphoramidites.[82]

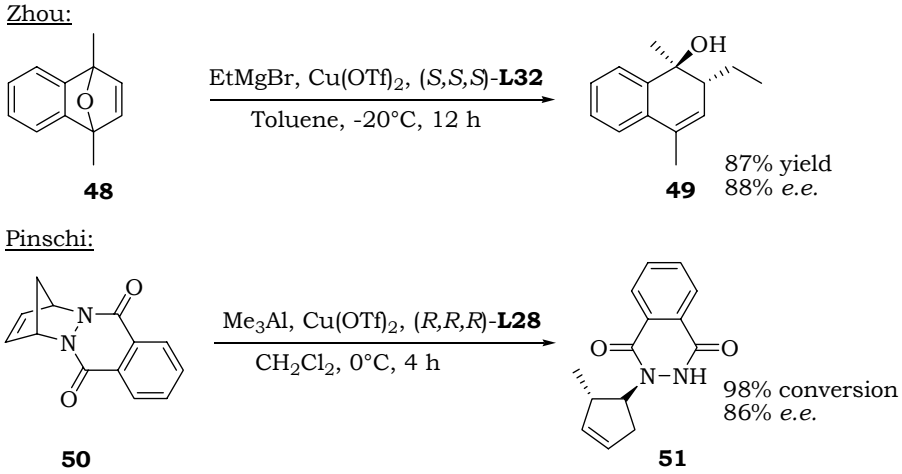
1.6.7 Ringopening

The groups of Pineschi and Zhou reported both the use of phosphoramidites in the ringopening reaction of cyclic derivatives employing either Grignard reagents, alkylzinc or alkylaluminium reagents.[83] Both groups obtained excellent regioselectivities in favor of the *anti*-products with maximum enantioselectivities of 86% and 88% (Scheme 1.17).

§ NaBARF = Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

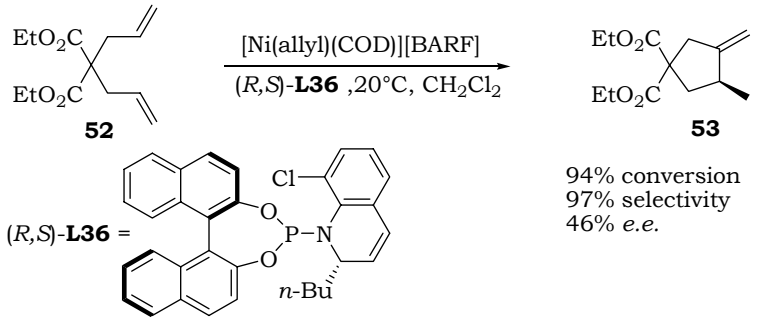
1.6.8 Cycloadditions

Monodentate phosphoramidites have also proven to be versatile ligands in a series of cyclization reactions. Mezzetti and co-workers reported an asymmetric cyclopropanation of substituted styrenes with half-sandwich Ru-complexes. [84] The enantioselectivities obtained were reasonable, but the selectivity towards the cis or the trans product was bad. Another drawback of this reaction was the low conversion.



Scheme 1.17: Cu-catalyzed ringopening reactions with phosphoramidites.[83]

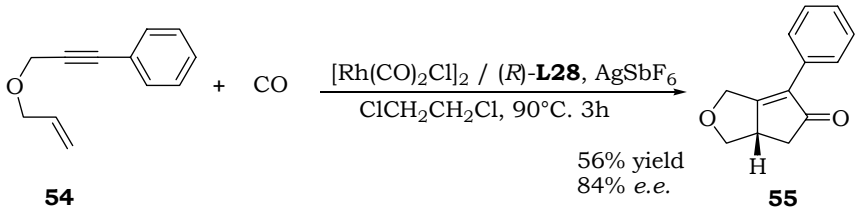
Böing *et al.* applied monodentate phosphoramidites in the Ni-catalyzed cycloisomerization of diethyl diallylmalonate (**52**).[85] Unfortunately, whereas the selectivity towards the desired product was good, the obtained enantioselectivities were rather poor (Scheme 1.18). The *e.e.* could be increased using a Wilke's bidentate azophospholene ligand.[86] In the Co-catalyzed [6+2] cycloaddition of cycloheptatriene with a terminal alkyne an enantioselectivity of 74% was reported with a chemical yield of 91%.[87]



Scheme 1.18: Ni-catalyzed cycloisomerization with phosphoramidites.[85]

1.6.9 Pauson-Khand reaction

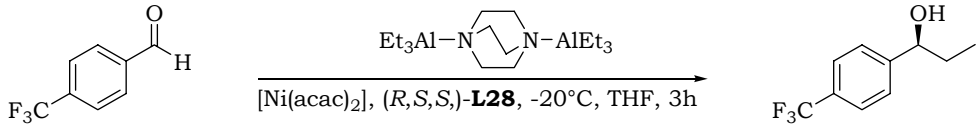
The earlier mentioned spiro phosphoramidites, developed by Zhou and co-workers, have also been successfully applied in the Rh-catalyzed asymmetric Pauson-Khand reaction.[88] Respectable enantioselectivities have been obtained, with modest yields (Scheme 1.19). Konya *et al.* reported the Co-catalyzed Pauson-Khand reaction with a series of BINOL-based monodentate phosphoramidites.[89] The yields were modest whereas the enantioselectivities were low.



Scheme 1.19: Rh / Spiro phosphoramidite catalyzed Pauson-Khand reaction.[88]

1.6.10 1,2-Additions

Woodward and co-workers reported a new and remarkably stable (Me_3Al)·DABCO adduct.[90] This new trialkylaluminium adduct has been employed successfully in the Ni-catalyzed 1,2-addition to aldehydes, using monodentate phosphoramidite (*R,S,S*)-**L28** as a chiral ligand. Excellent enantioselectivities have been achieved with good yields (Scheme 1.20).



56 — 90% yield, 95% *e.e.* — **57**

Scheme 1.20: Ni-catalyzed 1,2-addition.[90]

1.7 Aim and outline of this thesis

As described above, rhodium-catalyzed hydrogenation is a versatile, clean and atom economic method[91] for the production of enantioselective compounds. In recent years monodentate phosphoramidite ligands have proven to be excellent ligands for this reaction. Although all benchmark substrates can be hydrogenated in high enantioselectivities and with high turn-over numbers, the demand for new ligands remains, since there are still classes of substrates which can not be hydrogenated with good enantioselectivities or high reaction rates. More interesting however is the study of new substrates. The aim of this thesis is the development of new ligands / catalysts as well as substrates for the rhodium-catalyzed hydrogenation.

Chapter 2 describes the synthesis and application of new catechol-based phosphoramidites. These new ligands were effective in the hydrogenation of a number of benchmark substrates. In chapter 3 the synthesis and application of a water-soluble phosphoramidite, PegPhos, is described. Good enantioselectivities were obtained in the hydrogenation of *N*-acetyl α-dehydroalanine (**9**). The synthesis of diamidophosphites has been described in chapter 4. These ligands turned out to be very sensitive.

Low conversions and enantioselectivities have been obtained in the hydrogenation of a series of benchmark substrates. Chapter 5 describes the asymmetric hydrogenation of *α,β*-unsaturated acids using a mixed ligand system of a chiral phosphoramidite and an achiral phosphine. The powerful method of making libraries of phosphoramidites and screening those libraries has been used in the asymmetric hydrogenation of a new class of substrates, *i.e.* β^2-dehydroamino acids. The results are described in chapter 6. Finally, the results of screening a new class of phosphoramidites, based on phenols, on benchmark substrates is described in chapter 7.

1.8 References

[1] For this, the first Nobel Prize in chemistry was awarded to Jacobus van 't Hoff in 1901. See also: http://nobelprize.org/chemistry/laureates/1901/hoff-bio.html.

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[4] Later results showed that administration of enantiomerically pure Softenon did not help, since Softenon racemizes in the human body.

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Chapter 2
Catechol-based Phosphoramidites

In this chapter the synthesis and application of catechol-based phosphoramidites in rhodium-catalyzed hydrogenations are described. Ee's up to 99% were obtained in the asymmetric hydrogenation of enamides and dehydroamino acids.

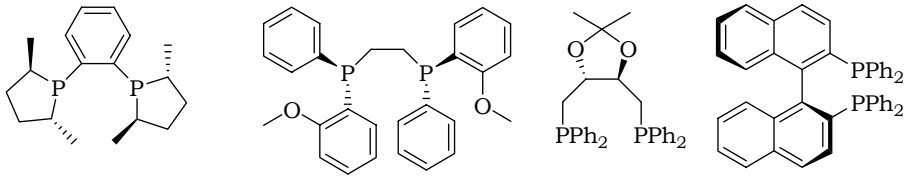
Part of this chapter has been published:

Hoen, R.; Van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; De Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, *6*, 1433-1436

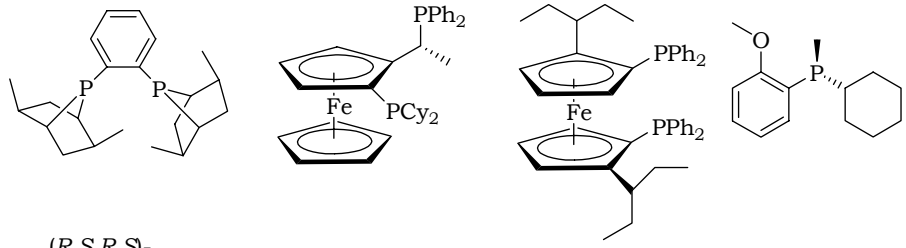
2.1 Introduction

2.1.1 Bidentate ligands for asymmetric rhodium-catalyzed hydrogenations

The rhodium-catalyzed asymmetric hydrogenation of enamides is a key method to synthesize enantiomerically pure amino acids and amines.[1] The majority of successful ligands used in this reaction is bidentate in nature,[2] *e.g.* DuPhos (**L1**)[3], DiPAMP (**L2**)[4], DIOP (**L3**)[5], BINAP (**L4**)[6], PennPhos (**L5**)[7], and ferrocenyl-based ligands, such as JosiPhos (**L6**)[8], and FerroPhos (**L7**)[9] (Figure 2.1). With the exception of CAMP (**L8**)[10], limited success was obtained with monodentate ligands. These ligands were considered not particularly effective since they lack the possibility to form chelating complexes with the metal.



(*R*,*R*)-Me-DuPhos (**L1**) (*S*,*S*)-DIPAMP (**L2**) (*S*,*S*)-DIOP (**L3**) (*S*)-BINAP (**L4**)

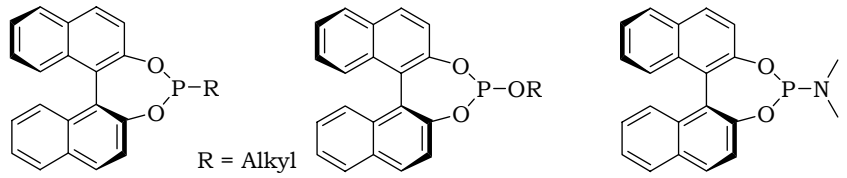


(*R*,*S*,*R*,*S*)-Me-PennPhos (**L5**) (*R*)-(*S*)-Josiphos (**L6**) (*S*,*S*)-FerroPhos (**L7**) (*S*)-CAMP (**L8**)

Figure 2.1: Successful bidentate ligands.

2.1.2 Monodentate ligands for asymmetric rhodium-catalyzed hydrogenations

After nearly 30 years of asymmetric hydrogenation it was unequivocally demonstrated in 2000 that bidentate chiral ligands are not a *conditio sine qua non* to reach high enantioselectivities. Three groups showed that monodentate phosphonites (**L9**), [11] phosphites (**L10**) [12] and phosphoramidites (**L11**)[13] can be applied successfully as chiral ligands in the rhodium-catalyzed asymmetric hydrogenation providing excellent enantioselectivities (Figure 2.2). A major advantage of these monodentate ligands is that they can be prepared in one or two steps at low costs, which makes variations easy (see also Scheme 2.1).



Phosphonites (**L9**) Phosphites (**L10**) Phosphoramidites (**L11**)

Figure 2.2: Monodentate Phosphonites, Phosphites and Phosphoramidites.

Most successful monodentate ligands recently introduced consist of a chiral diol backbone, with another chiral or achiral moiety attached to phosphorus.[14] The chirality of the backbone dictates in nearly all cases the chirality of the product.[12] The chirality of the other moiety at phosphorus is found to be less important. Illustrative is that one of the most effective monodentate ligands for hydrogenation reactions, the commercially available[15] phosphoramidite MonoPhos™ (**L11**), consists of only the chiral BINOL part an achiral *N,N*-dimethyl amine moiety. A few reports on alternative ligands using chiral backbones, such as biphenyls or spiro compounds, have appeared.[16]

2.1.3 Goal of this research

From earlier results it was evident, that in the case of BINOL derived phosphoramidites, a small amine moiety is favored for the hydrogenation of dehydroamino acids.[13,14c] Later results showed that the introduction of a piperidine moiety improved the enantioselectivity of the hydrogenation of a variety of substrates even further.[17] In this chapter a new class of monodentate phosphoramidites, based on an *achiral* catechol backbone is described. In this case the chirality of the products must be dictated solely by the chirality of the amine moiety. Not only is the chiral moiety an amine instead of the diol, but also the bulkiness of the diol backbone is reduced as a planar catechol is present whereas the size of the amine moiety is increased in the new ligand compared to MonoPhos™ (**L11**).

2.2 Synthesis of phosphoramidites

2.2.1 Synthesis of BINOL-based phosphoramidites

In general three methods are used to synthesize monodentate phosphoramidites based on BINOL (**1**) (Scheme 2.1).[17,18] In the first method BINOL (**1**) is reacted with PCl_3 to yield the corresponding phosphorochloridite (**2**). The phosphorochloridite is then reacted with a primary or secondary amine to form the phosphoramidite. In some cases when sterically demanding amines are introduced the more reactive lithium amide of the amine is reacted with the phosphorochloridite (**2**).* The second method converts BINOL in MonoPhos™ (**L11**) by reacting it with HMPT†. Different phosphoramidites can be obtained by amine exchange with MonoPhos™ (**L11**).[18] The third method is the so-called reversed synthetic approach.[19] In the first step the amine is reacted with PCl_3 to form the corresponding dichlorophosphino amine, which reacts subsequently with the diol to form the corresponding phosphoramidite.

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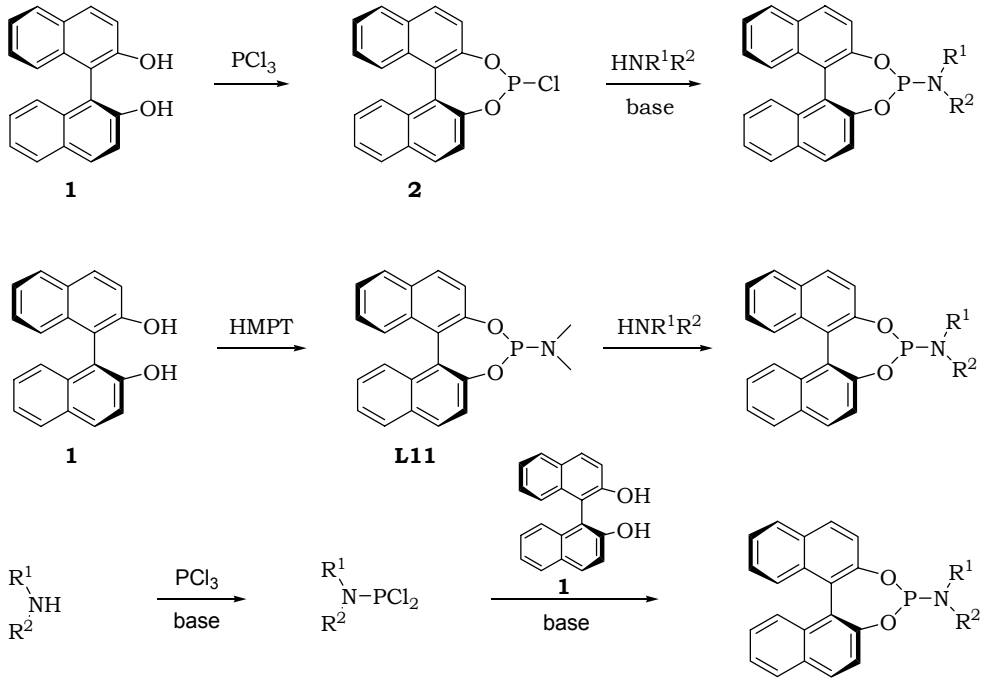
* The Li-amides were prepared by reaction of the amine with *n*-BuLi.

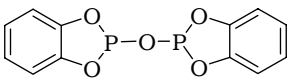
† HMPT is hexamethylphosphorus triamide



Scheme 2.1: Synthesis of Phosphoramidites.[18]

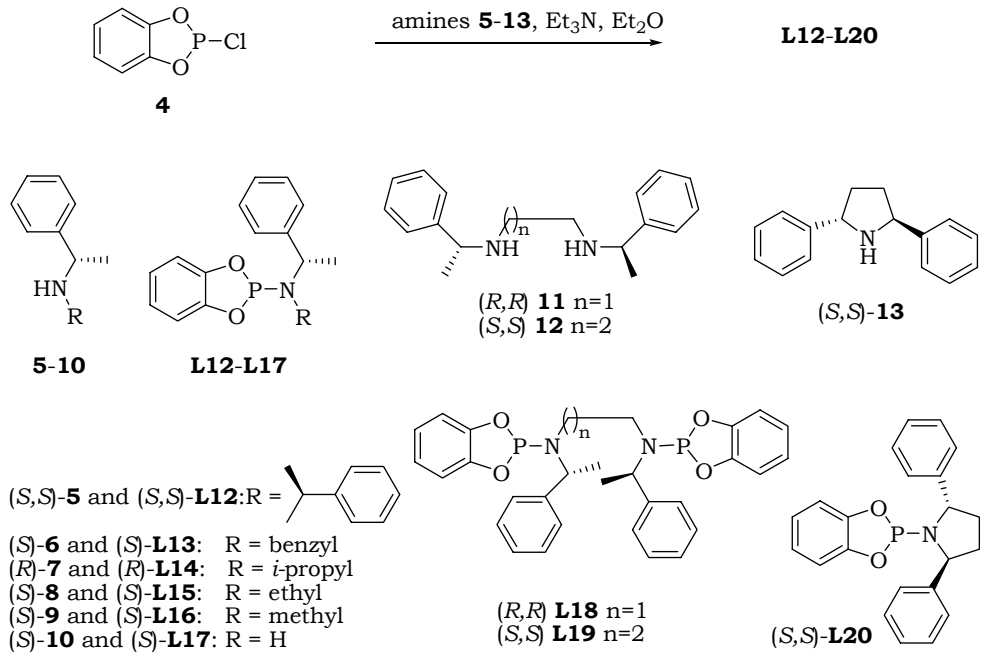
2.2.2 Synthesis of catechol-based phosphoramidites

Since *o*-phenylene phosphorochloridite (**4**) is commercially available, the choice was made to use the first method for synthesizing catechol-based phosphoramidites. Initial attempts using the Li-amide of the corresponding amines afforded the ligands in low yield. A side product was obtained with a ^{31}P signal at 128 ppm, independent of the amine that was used. Phosphoramidites in general have ^{31}P signals between 140 and 150 ppm.[17a] It is assumed that the formed side-product is pyrophosphite **3**, since it's known from literature [20] that phosphorochloridites can react with water under basic conditions to form pyrophosphites. The reactions were performed in THF, which might have contained traces of water. When the solvent was switched to diethyl ether or methyl *t*-butyl ether and the base was replaced by Et_3N, the desired phosphoramidites could be obtained in moderate yields (21%-48%) after



3

work up and column chromatography. The catechol-based ligands are in general more sensitive to hydrolysis than BINOL-based phosphoramidites. A considerable lost of product was observed after column chromatography on silica gel presumably due to hydrolysis during chromatography. A variety of easily accessible chiral amines, based on (*S*)-(-)-1-phenylethylamine, were used in the preparation of ligands **L12**-**L17**. The cyclic analogue **L20** of ligand **L12** was obtained from the corresponding chiral amine **13**, which could be synthesized in four steps from commercially available *trans*-1,2-dibenzoylethylene.[21] For comparison also bidentate ligands **L18** and **L19** were examined (Scheme 2.2). All ligands were obtained as sticky colorless oils, with exception of **L12** and **L20**, which were obtained as white powders. ^{31}P-NMR spectra showed single peaks in the range of 140-150 ppm, typically for phosphoramidites. Additional information was obtained by mass spectroscopy and ^{1}H- and ^{13}C-NMR spectroscopy.



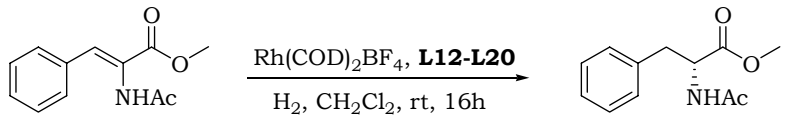
Scheme 2.2: Synthesis of catechol-based phosphoramidites.

2.3 Catechol-based phosphoramidites in rhodium-catalyzed hydrogenations

2.3.1 Enantioselective hydrogenation of *N*-acyl dehydrophenylalanine methyl ester (14)

As a benchmark reaction, the ligands were tested in the rhodium-catalyzed asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (**14**) under standard conditions. Standard conditions are: 0.2 mmol of substrate, 1 mol% of catalyst (**L**:Rh = 2:1) in 4 ml CH_2Cl_2 at room temperature and 5 bar of H_2 pressure. The results are depicted in Table 2.1.

Table 2.1: Asymmetric hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (**14**) catalyzed by Rh-phosphoramidite ligand systems derived from catechol.



14 **15**

Entry	*Ligand*	*Conversion*[a,b]	*E.e.*[c]
1	**L12**	0	-
2	**L13**	60	<3
3	**L14**	45	<3
4	**L15**	100	<3
5	**L16**	60	<3
6	**L17**	90	<3
7	**L18**	100	5[d]
8	**L19**	100	32 [d]
9	**L20**	100	92 [d]

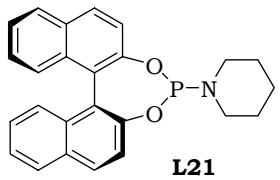
a) Reactions performed under standard conditions; 0.2 mmol of substrate, 1 mol% catalyst (**L**:Rh = 2:1) in 4 ml CH_2Cl_2 at RT and 5 bar of H_2 pressure; b) Conversions determined by ^{1}H-NMR, no side products were observed in addition to product and/or starting material; c) *E.e.* determined by chiral GC (CP Chiralsil-L-Val) d) Product has the *R* configuration, except when **L18** is used (see experimental section for assignment).

The catalysts based on ligands **L13** to **L17** gave modest to full conversions, while the ligand **L12** based on a sterically demanding amine,

surprisingly, gave no conversion at all. The enantiomeric excesses are in all cases disappointing (entries 1-6, Table 2.1). In sharp contrast however, is the excellent yield and enantioselectivity of >92% reached with ligand **L20** (entry 9). Although **L12** and **L20** have a similar kind of structure, a remarkable difference in activity was observed by introduction of a ring structure in the ligand. The bidentate ligands **L18** and **L19** induced full conversion but rather poor *e.e.*'s although a longer spacer in the ligand resulted in a slightly higher *e.e.* (entries 7 and 8).

2.3.2 Enantioselective hydrogenation of a variety of substrates

A variety of substrates was tested to expand the scope of the catalytic hydrogenation employing **L20**. As shown in Table 2.2, other α-amino acid precursors gave full conversions with modest *e.e.'s* (entries 1 and 2, Table 2.2). In contrast, *β*-amino acid precursor **18** gave no conversion at all using CH_2Cl_2 as the solvent (entry 3). When the reaction was performed in *i*-PrOH, 80% *e.e.* was obtained at 40% conversion (entry 4). In earlier studies it was shown that *i*-PrOH is the best solvent for the Rh-phosphoramidite catalyst system in the hydrogenation of *β*-amino acid precursors with a *Z*-configuration.[22] Elimination of the internal hydrogen bond by *i*-PrOH has been postulated as the origin of this change in reactivity.[23] Enamides **19** and **20** were fully converted and the *e.e.'s* were good to excellent (entries 5 and 6). As expected, the imines **21** and **22** were not converted. Although carbamate **23** was hardly converted, the selectivity was negligible.

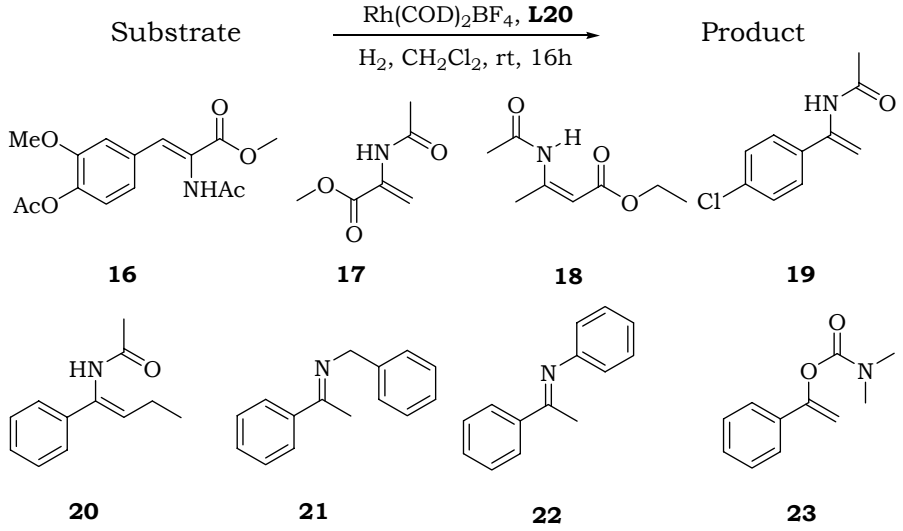


L21

This initial study revealed that **L20** is comparable to MonoPhos™ (**L11**) with respect to selectivity in the hydrogenation of α-amino acid precursors. In the hydrogenation of enamides, however, higher enantioselectivities are observed with a remarkable 99% *e.e.* for the hydrogenation of **20**.[13,14r] Later results revealed that PipPhos (**L21**) gives in most cases almost perfect selectivity for the α-amino acid precursors as well as the enamides.[17a] So far no good results have been obtained for the hydrogenation of imines with monodentate phosphoramidites. Monodentate secondary phosphine oxides, on the other hand, have proved to be much more successful (see also chapter 1).[24] The results with

carbamate **23** are comparable to those obtained with MonoPhos™ (**L11**). It appeared that specifically in the hydrogenation of the carbamate the structure of the phosphoramidite is crucial. Introduction of a six-membered ring at the amine moiety raised the rate of the reaction as well as the enantioselectivity.[25] With these results in hand we decided to screen series of enamides.

Table 2.2 : Asymmetric hydrogenation of a variety of substrates catalyzed by Rh-phosphoramidite (**L20**) catalyst.

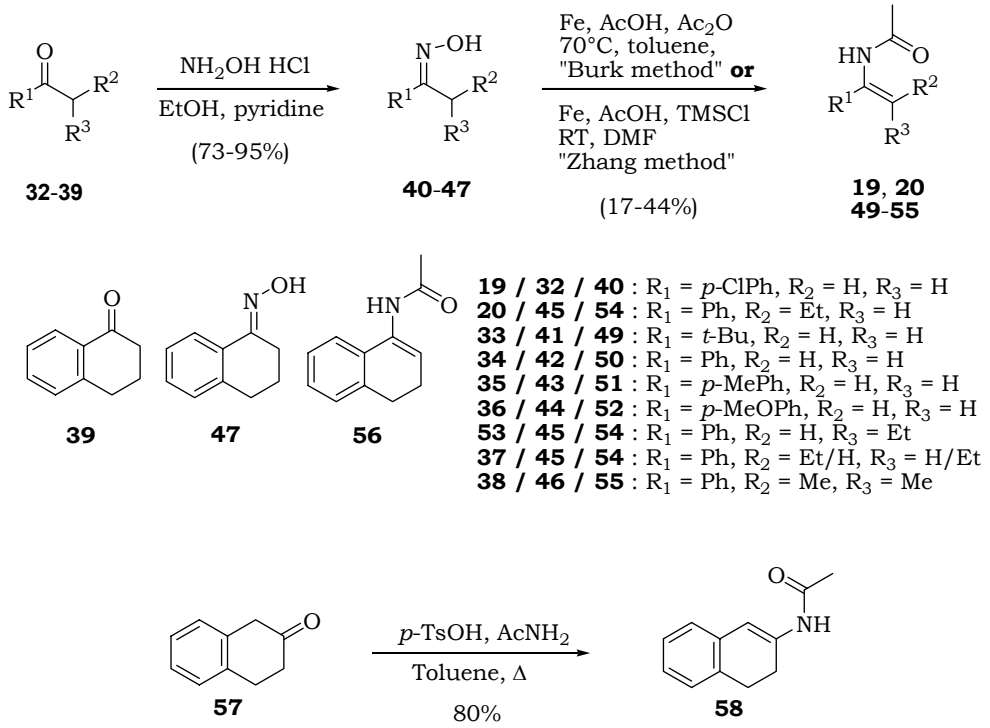


Entry	*Substrate*	*Product*	*Conversion* [a,b]	*E.e.*[c, d]
1	**16**	**24**	100	89
2	**17**	**25**	100 (>99)	66
3	**18**	**26**	0	-
4[e]	**18**	**26**	40	80
5	**19**	**27**	100 (>98)	89
6	**20**	**28**	100 (>99)	99
7	**21**	**29**	0	-
8	**22**	**30**	0	-
9	**23**	**31**	33	6

a) Reactions performed under standard conditions; b) Conversions determined by ^{1}H-NMR, no side products were observed in addition to product and/or starting material; isolated yields between brackets; c) *E.e.'s* determined by chiral GC or HPLC (CP Chiralsil-L-Val, CP Chiralsil-Dex CB, Chiralcel OD); d) All products had the R configuration e) Reaction was performed in *i*-PrOH.

2.3.3 Synthesis of enamides

The substrates were synthesized, starting from the corresponding oxims, [26] using methods developed by Zhang[7b] and Burk (Scheme 2.3). [27, 28] Although easy synthesis and high yields are claimed, the purification of the compounds is not straightforward. For most compounds extensive column chromatography, washing and recrystallization was needed.



Scheme 2.3: Synthesis of enamides.

In no case the reported yields could be reproduced. Substrate **54** was obtained as a 3:2 mixture of *E*- and *Z*-isomers which could be separated by column chromatography. Substrate **58** could be made in a one step procedure from the corresponding ketone with *p*-toluenesulfonic acid and acetamide in good yields.[29] This method did not work for other substrates as no conversion was observed.

2.3.4 Asymmetric hydrogenations of enamides with a Rh-phosphoramidite (L20) complex

The series of enamides was screened in two solvents at 5 and 25 bar of hydrogen pressure to examine the scope of the asymmetric hydrogenation. The results are depicted in Table 2.3.

Table 2.3 : Results of the asymmetric hydrogenation of enamides with Rh-Phosphoramidite (**L20**) complex.[a]

Entry	*Substrate*	*Product*	*E.e.* [b-e] CH_2Cl_2 *5 bar*	*E.e.* [b-e] CH_2Cl_2 *25 bar*	*E.e.*[b-e] *EtOAc 25 bar*
1	**49**	**59**	63	70	26
2	**50**	**60**[f]	92	93	96.5
3	**51**	**61**	95	94	97
4	**52**	**62**	97	97	97
5	**19**	**27**	89	89	94
6	**20**	**28**	99	>99	>99
7	**53**	**28**	90	88	80
8	**54**[g]	**28**	92	93	84
9	**55**	**63**	9 (3.5)	20 (6)	<3 (14)
10	**56**	**64**	35 (48)	35 (95)	27
11	**58**	**65**	4 (14)	9 (38)	35 (40)

a) Reactions performed in 4 mL solvent with 0.2 mmol substrate and 1 mol% of catalyst at RT under a H_2 atmosphere for 16 h; b) Conversions determined by ^{1}H-NMR, no side products were observed in addition to product and/or starting material; c) *E.e.'s* determined by chiral GC (CP Chiralsil-Dex CB); d) Conversions are between brackets if reactions were not run to completion; e) In all cases the *R* configuration of the product was obtained, except for products **65** and **59**; f) Isolated yield for **60** was >99% g) A mixture with a 3:2 ratio of E and Z alkene was used.

With the exception of **55**, containing a tetrasubstituted alkene, and the bicyclic systems **56** and **58** (entries 9-11, column 4, Table 2.3), all substrates gave full conversion. The enantioselectivity is lower when R_1 is an alkyl group instead of an aryl group, (compare entries 1 and 2, column 4). This can be due to an increase of steric hindrance, although this seems to be a common feature of this catalytic system, since similar results were observed in the hydrogenation of the α-amino acid precursors (compare entry 9, Table 2.1 and entry 2, Table 2.2). Favorable π-π interactions between the aromatic moiety of the substrate and the ligand might be another reason for this observation. Different substituents on the aromatic ring seem to have hardly any influence on the enantioselectivity (entries 2-

5, column 4). Tri-substituted alkenes gave good to excellent enantioselectivities. The best results were obtained with enamides with a *Z*-configuration (entries 6 and 7, column 4) while an *E*/*Z* mixture gave the calculated average of the enantioselectivities for both isomers (entry 8, column 4). Tetra-substituted alkenes and bicyclic systems are not suitable substrates for this new catalytic system. Low conversions and moderate enantioselectivities were obtained (entries 9-11, column 4). High enantioselectivities for these substrates have been obtained with a variety of bidentate phosphines.[30] Reasonable enantioselectivities for alkene **56** were obtained using MonoPhos™ (**L11**) at –20°C.[31]

An increase of the pressure to 25 bar had no influence on the enantioselectivity although the conversion did increase.[‡] Only in the case of the tetra-substituted alkene and the bicyclic systems derived from *β*-tetralone the *e.e.* increased (entries 9 and 11).

The use of EtOAc as solvent resulted in higher enantioselectivities for most of the substrates (Table 2.3, column 6). Surprisingly, the only exceptions are those with R_1 is a *t*-Bu group (entry 1) or when R_3 (Scheme 2.3) is not hydrogen (entries 7-10).

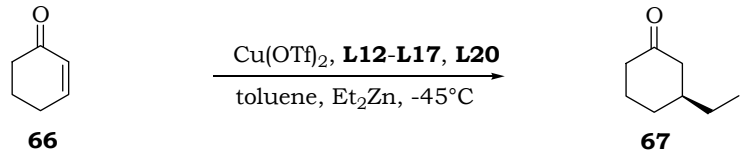
2.4 Catechol-based monodentate phosphoramidites in the copper-catalyzed conjugate addition of diethylzinc to cyclohexenone

Ligand **L12** has been reported to induce 78% *e.e.* in the copper-catalyzed conjugate addition of Et_2Zn to cyclohexenone (**66**).[18] Ligands **L13**-**L20** were also tested in this reaction. The results are depicted in Table 2.4.

The results from Table 2.4 show that the bulkiness of the ligand is very important. Decreasing the size of the amine in the ligands lowers the *e.e.* dramatically.

[‡] Reactions were run overnight, although in most cases reactions were completed in 4 h at 5 bar and in 2 h at 25 bar of hydrogen pressure

Table 2.4: The copper-catalyzed conjugated 1,4-addition of diethylzinc to cyclohexenone with **L12**-**L17** and **L20**.[a]



66 **67**

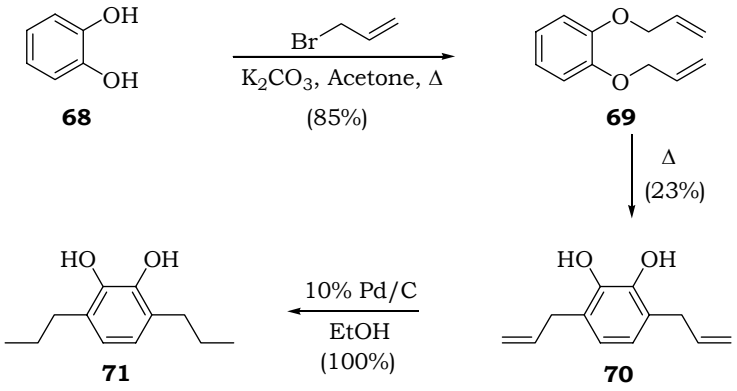
Entry	*Ligand*	*E.e.*[b]	*Entry*	*Ligand*	*E.e.*[b]
1	**L12**	78	5	**L16**	2
2	**L13**	15	6	**L17**	1
3	**L14**	48	7	**L20**	35
4	**L15**	6			

a) Reactions were performed with 0.5 mmol of substrate, 2 mol% of $Cu(OTf)_2$, 4 mol% of ligand and 1.1 equivalents of Et_2Zn in 10 ml toluene b) *E.e.*'s were determined by chiral GC; Astec G-TA, 30 m x 0.25 mm, He-flow 1.0 ml / min, isocratic 95°C T_r = 25.8 min (S), T_r = 27.2 min (R).

2.5 A new series of catechol-based phosphoramidites

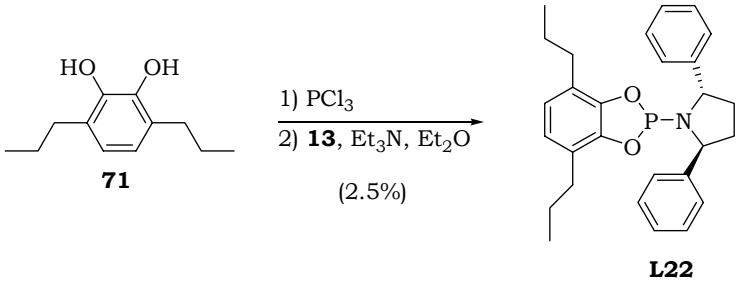
2.5.1 Synthesis of ligands L22-26

With these results in hand, a new series of catechol-based monodentate phosphoramidites was prepared. Ligand **L22**, with two *n*-propyl substituents on the catechol moiety, was synthesized to investigate the influence of steric hindrance due to alkyl groups at the ortho-positions. Catechol (**68**) was reacted with 2 equivalents of allyl bromide to form the corresponding diallylether (**69**). [32] The diallylether was subsequently rearranged to form **70** in only 23% yield.[32] In addition to the desired product, a mixture of side-products was obtained, the composition of which has not been identified. Reduction of the double bonds of the allyl moieties with H_2 and 10% Pd/C yielded **71** quantitatively (Scheme 2.4).



Scheme 2.4: Synthesis of **71**.

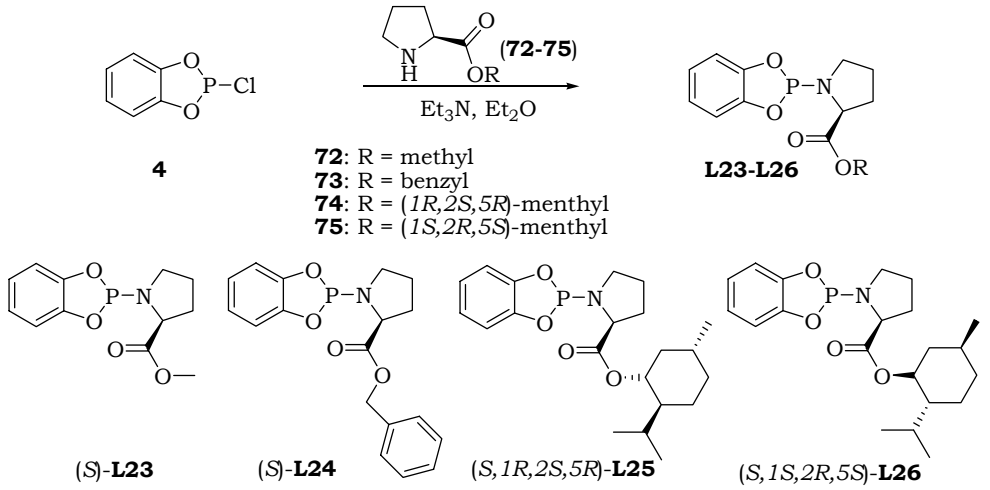
L22 could be synthesized by refluxing **71** in PCl_3 to provide the corresponding phosphorochloridite (not shown) (Scheme 2.5). The phosphorochloridite was reacted with amine **13** in the presence of Et_3N to provide **L22** in a very low 2.5% yield (not optimized). The low yield is mainly caused by decomposition of **L22** on the column during chromatographic purification.



Scheme 2.5: Synthesis of **L22**.

A series of ligands based on proline esters was synthesized, as an alternative to the rather difficult to synthesize cyclic amine **13** (Scheme 2.6). Amines **72**-**75** could be synthesized in a one pot procedure from the commercially available (*S*)-proline by a literature procedure.[34] Ligands **L23**-**L26** were synthesized according the procedure described in Scheme 2.2 in 30-60% yield. ^{31}P-NMR spectra showed single peaks in the range of 140-150 ppm, typically for phosphoramidites. Additional information was obtained by mass spectroscopy and ^{1}H- and ^{13}C-NMR spectroscopy.

A difference between **L20** and **L23**-**L26** is the degree of symmetry. **L20** based on catechol and symmetrical 2,5-disubstituted pyrolidine is C_2-symmetric, while **L23**-**L26** are based on non-symmetrical proline esters which makes these ligands C_1-symmetric.



Scheme 2.6: Synthesis of ligands **L23**-**L26**.

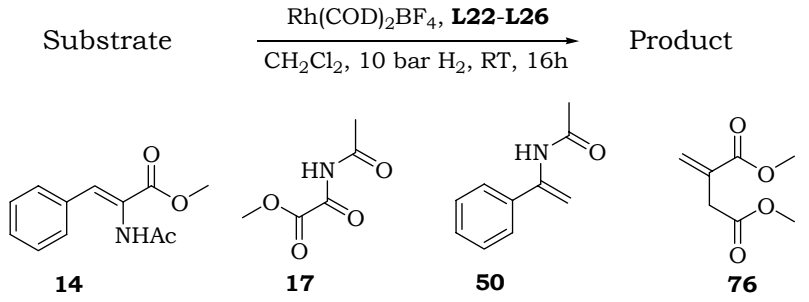
2.5.2 Hydrogenation of benchmark substrates using L22-L26 as ligands

Monodentate phosphoramidites **L22**-**L26** were tested in the rhodium-catalyzed asymmetric hydrogenation of a set of 4 benchmark substrates *i.e.,* **14**, **17**, **50** and **76** (*vide infra*). The reactions were run at 10 bar of hydrogen pressure with 1 mol % of catalyst for 16h. The results are depicted in Table 2.5.

Introduction of *n*-propyl groups on the catechol moiety decreases the enantioselectivity as well as the conversion (compare entry 9, Table 2.1; entry 2, Table 2.2; entry 2, Table 2.3 vs. entry 1, Table 2.5). The *e.e.'s* obtained for the hydrogenation of substrate **76** with ligands **L22**-**L26** are very low. In all cases incomplete conversion was obtained (entries 1-5, Table 2.5). The enantioselectivities obtained in the hydrogenation of amino acid derivatives **14** and **17** with ligands **L23**-**L26** are rather poor compared to the results obtained with **L20** (entries 2-5, Table 2.5 vs. entry 9, Table 2.1; entry 2, Table 2.2). The best results with **L23**-**L26** were obtained in

the hydrogenation of enamide **50**, although the enantioselectivities are still lower than those with **L20** (entries 2-5, Table 2.5 vs. entry 2, Table 2.3).

Table 2.5: Rh-catalyzed asymmetric hydrogenation with **L22**-**L26**.[a]



14 **17** **50** **76**

Entry	*Ligand*	*E.e. after hydrogenation of substrate*[b,c,d,e]			
		14	**17**	**50**	**76**
1	**L22**	18 (19)	20 (45)	14 (22)	7 (17)
2	**L23**	27	42	69	3 (45)
3	**L24**	38	3	65	15 (43)
4	**L25**	6	22	69	7 (54)
5	**L26**	35	31	60	12 (50)

a) Reactions performed in 4 mL solvent with 0.2 mmol substrate and 1 mol% of catalyst at RT under a H_2 atmosphere of 10 bar for 16 h b) Conversions determined by ^{1}H-NMR, besides product and/or starting material no side products were observed c) E.e.'s determined by chiral GC d) Conversions are between brackets if reactions were not run to completion e) In all cases the R enantiomer was obtained, except for product of substrate **76**.

The size of the R-group (Scheme 2.6) has hardly any influence on the enantioselectivity of the hydrogenation products. Neither does the introduction of additional stereocenters as in **L25** and **L26** have a significant effect. The *e.e.* of the products is mainly defined by the stereocenter of proline, since no pronounced matched/missmatched effect has been observed and the absolute configuration of the products is the same for hydrogenations performed with **L25** and **L26**.

2.6 Conclusion

In this chapter a successful synthesis of catechol-based monodentate phosphoramidites has been described. These ligands showed good results in the rhodium-catalyzed asymmetric hydrogenation of a variety of pro-chiral alkenes. In particular, ligand **L20**, based on catechol and enantiopure *trans*-2,5-diphenylpyrolidine, showed excellent results in the hydrogenation of enamides. Up to 99% of *e.e.* has been reached in the asymmetric hydrogenation of **20**. **L20**, together with **L21**, are among the best ligands reported so far for the enantioselective hydrogenation of enamides. [14,17a]

The catechol-based ligands have also been tested in the Cu-catalyzed conjugate addition of diethylzinc. Modest *e.e.'s* have been obtained. The best ligand was **L12**, which induced an *e.e.* of 78%.

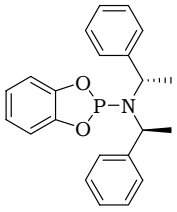
2.7 Experimental section

General remarks:

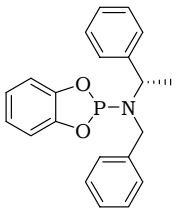
All reactions were performed in a dry argon atmosphere using standard Schlenk techniques. Et_2O (Na), CH_2Cl_2 (CaH), EtOAc (boiling chips), toluene (Na) and pentane (boiling chips) were distilled before use. Substrate **14** was made according a literature procedure.[33] Substrates **17** and **76** are commercially available. Michel van den Berg is gratefully acknowledged for substrate **16**. Diego Peña is gratefully acknowledged for substrate **18**. Xiao-Bin Jiang is gratefully acknowledged for substrates **21**-**23**. Leggy Arnold is gratefully acknowledged for ligand **L12** and amines **7** and **8**. Amines **8**, **9**, **11**-**13** and **72**-**75** were made according literature procedures.[34] Amine **10** is commercially available. Ketones **32**-**39** were commercially available.
^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded on a Varian Gemini-200, Varian VXR-300 or a Varian Mercuri Plus. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of $CHCl_3$ (^{1}H-NMR: δ 7.26; ^{13}C-NMR: δ 77.0); DMSO (^{1}H-NMR: δ 2.49; ^{13}C-NMR: δ 39.5) or relative to an external standard for ^{31}P (H_3PO_4 at δ 0.0). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), b (broad). Optical rotations were measured with a Perkin Elmer 241 polarimeter. Column chromatography was performed using silica gel (Aldrich 60, 230-400 mesh). Mass spectra (HRMS) were recorded on an AEI MS-902.

General procedure for the synthesis of the ligands:

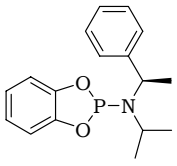
To a solution of 1.5 g (8.60 mmol) of *o*-phenylenephosphorochloridite (**4**) and 0.87 g (8.60 mmol) of Et_3N in 5 ml of Et_2O was added a solution of 8.60 mmol of the appropriate amine in 5 ml Et_2O at 0°C. This suspension was warmed to RT and stirred for 1.5 h. The reaction mixture was filtered over Celite. The filtrate was concentrated. The ligand was purified by filtration over a short plug of silica gel (eluent *n*-pentane:EtOAc 10:1).



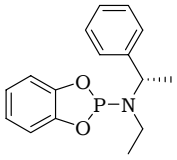
(*S*,*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-bis-(1-phenyl-ethyl)-amine (L12): White solid. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.26-7.14 (m, 12H), 7.01-6.98 (m, 2H), 4.45 (m, 2H), 1.79 (dd, *J* = 1.8 Hz, 7.1 Hz, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.8, 142.0, 129.1, 127.9, 127.7, 127.6, 126.9, 121.7, 53.3, 53.0, 22.4, 22.2; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ = 151.9; **HRMS** calcd. for $C_{22}H_{22}NO_2P$ 363.138 found 363.138; **$[\alpha]_D^{20}$** = -264° (c= 0.79, $CHCl_3$).



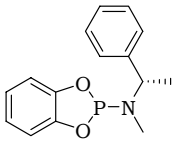
(*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-benzyl-(1-phenyl-ethyl)-amine (L13): The ligand was obtained as a colorless sticky oil in 25% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ =7.35-7.13 (m, 10H), 6.96-6.78 (m, 4H), 4.34-4.29 (m, 1H), 3.69 (ddd, *J* = 6.8 Hz, 15.7 Hz, 33.8 Hz, 2H), 1.43 (dd, *J* = 1.8 Hz, 7.1 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.7, 146.6, 146.5, 146.3, 141.9, 138.4, 128.5, 128.3, 128.1, 127.3, 127.2, 121.7, 111.4, 56.2, 55.9, 47.2, 47.1, 22.3, 22.1; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =146.1; **HRMS** calcd. for $C_{22}H_{22}NO_2P$ 349.123 found 349.122; **$[\alpha]_D^{20}$** = -21° (c= 1.17, $CHCl_3$).



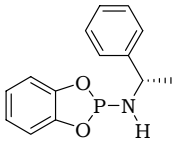
(*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-isopropyl-(1-phenyl-ethyl)-amine (L14): The ligand was obtained as a colorless sticky oil in 37% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ =7.42-7.22 (m, 5H), 7.04-6.95 (m, 2H), 6.90-6.81 (m, 2H), 4.43-4.37 (m, 1H), 3.18-3.05 (m, 1H), 1.54 (dd, *J* = 0.5 Hz, 7.1 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.7, 128.2, 127.6, 127.0, 121.6, 111.4, 52.5, 52.4, 46.5, 46.1, 26.3, 26.1, 25.1, 24.9, 20.7, 20.6; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ = 152.5; **HRMS** calcd. for $C_{17}H_{20}NO_2P$ 301.123 found 301.123; **$[\alpha]_D^{20}$** = +214° (c= 1.02, $CHCl_3$).



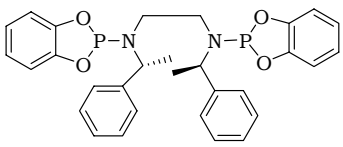
(*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-ethyl-(1-phenyl-ethyl)-amine (L15): The ligand was obtained as a colorless sticky oil in 36% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.45-7.28 (m, 5H), 7.06-6.89 (m, 4H), 4.73-4.65 (m, 1H), 2.79-2.64 (m, 2H), 1.69 (dd, *J* = 1.6 Hz, 7.2 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =146.7, 146.6, 146.4, 142.3, 142.3, 128.4, 127.1, 121.6, 111.2, 55.7, 55.1, 37.2, 37.1, 21.5, 21.2, 17.0, 16.9; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =149.5; **HRMS** calcd. for $C_{16}H_{18}NO_2P$ 287.108 found 287.108; **$[\alpha]_D^{20}$** = -65° (c= 1.36, $CHCl_3$).



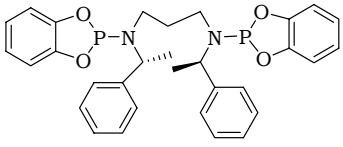
(*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-methyl-(1-phenyl-ethyl)-amine (L16): The ligand was obtained as a colorless sticky oil in 44% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.42-7.26 (m, 5H), 7.05-6.97 (m, 2H), 6.94-6.87 (m, 2H), 4.79-4.71 (m, 1H), 2.20 (d, *J* = 6.1 Hz, 3H), 1.59 (dd, *J* = 0.6 Hz, 7.0 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.7, 141.0, 128.4, 127.1, 121.6, 111.1, 55.0, 54.4, 26.2, 26.1, 18.8, 18.6; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =147.0; **HRMS** calcd. for $C_{15}H_{16}NO_2P$ 273.092 found 273.091; **$[\alpha]_D^{20}$** = -28° (c= 1.09, $CHCl_3$).



(*S*)-Benzo[1,3,2]dioxaphosphol-2-yl-(1-phenyl-ethyl)-amine (L17): The ligand was obtained as a colorless sticky oil in 38% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.36-6.78 (m, 9H), 4.21-4.06 (m, 1H), 3.84 (m, 1H), 1.86 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.0, 144.5, 128.3, 126.9, 125.6, 121.8, 121.7, 111.6, 11.3, 50.0, 25.2, 25.2; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =137.6; **HRMS** calcd. for $C_{14}H_{14}NO_2P$ 259.076 found 259.077; **$[\alpha]_D^{20}$** = -205° (c= 1.27, $CHCl_3$).

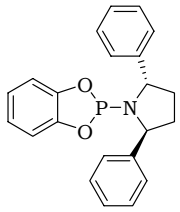


(*R,R*)-*N,N'*-Bis-benzo[1,3,2]dioxaphosphol-2-yl-*N,N'*-bis-(1-phenyl-ethyl)-ethane-1,2-diamine (L18): The ligand was obtained as a colorless sticky oil in 21% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.40-7.15 (m, 10H), 7.00-6.84 (m, 8H), 4.24-4.13 (m, 2H), 2.74-2.43 (m, 4H), 1.26 (d, *J* = 7.1 Hz, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.6, 141.7, 128.3, 127.2, 121.8, 111.5, 111.3, 55.2, 54.8, 44.5, 44.3, 20.5, 20.3; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =150.1; **HRMS** calcd. for $C_{30}H_{30}N_2O_4P_2$ 544.168 found 544.168; **$[\alpha]_D^{20}$** = -125° (c= 1.06, $CHCl_3$).



(*S,S*)-*N,N'*-Bis-benzo[1,3,2]dioxaphosphol-2-yl-*N,N'*-bis-(1-phenyl-ethyl)-propane-1,3-diamine (L19): The ligand was obtained as a colorless sticky oil in 29% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.43-7.25 (m, 10H), 7.00-6.82

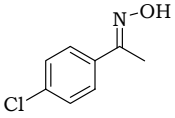
(m, 8H), 4.40-4.29 (m, 2H), 2.32-2.15 (m, 4H), 1.49 (dd, *J* = 1.7 Hz, 7.0 Hz, 6H), 1.53-1.21 (m, 4H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 146.0, 141.8, 128.4, 127.2, 127.1, 121.7, 111.2, 55.5, 55.0, 40.3, 40.2, 31.8, 21.5, 21.2; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =148.5; **HRMS** calcd. for $C_{31}H_{32}N_2O_4P_2$ 558.184 found 558.184; **$[\alpha]_D^{20}$** = +79° (c= 1.41, $CHCl_3$).



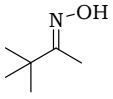
(*S,S*)-1-Benzo[1,3,2]dioxaphosphol-2-yl-2,5-diphenyl-pyrrolidine (L20): The ligand was obtained as colorless crystals in 46% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.26-7.11 (m, 10H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.75 (dt, *J* = 1.1 Hz, 7.7 Hz, 1H), 6.51 (dt, *J* = 1.1 Hz, 7.7 Hz, 1H), 5.95 (d, *J* = 7.7 Hz, 2H), 2.36-2.25 (m, 2H), 1.67-1.57 (m, 2H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =145.0, 128.1, 126.8, 126.1, 121.6, 121.2, 111.5, 110.3, 63.2, 63.1, 33.7; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =143.9; **HRMS** calcd. for $C_{22}H_{20}NO_2P$ 361.122 found 361.123; **Anal. Calc**. for $C_{22}H_{20}NO_2P$: C, 73.12 %; H, 5.58 %; N, 3.88 %, found: C, 73.09 %; H, 5.58 %; N, 3.89 %; **$[\alpha]_D^{20}$** = -104° (c= 0.79, $CHCl_3$).

General procedure for the synthesis of oximes:

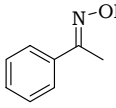
A mixture of 10 g ketone and 10 g (144 mmol) hydroxylamine (HCl salt) in 100 ml EtOH and 10 ml pyridine was refluxed overnight. The reaction mixture was concentrated and poured into 100 ml ice/water. The cooled (0°C) mixture was stirred for 45 min and filtered. The white precipitate was dissolved in 100 ml EtOAc and dried over Na_2SO_4. The mixture was filtered and concentrated to yield the corresponding oxime in 73-95% yield. The product was used in the next step without any purification.



1-(4-Chloro-phenyl)-ethanone oxime (40): The oxime was obtained as a white solid in 92% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 9.58 (bs, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 2.29 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =155.1, 135.3, 134.8, 128.7, 127.3, 12.2; **HRMS** calcd. for C_8H_8ClNO 162.029 found 162.028.

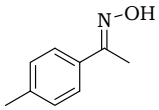


3,3-Dimethyl-butan-2-one oxime (41): The oxime was obtained as a white solid in 73% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 9.39 (bs, 1H), 1.88 (s, 3H), 1.13 (s, 9H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =163.9, 37.2, 27.4, 10.0; **MS** m/z 116 (M+1), 133 (M+18).

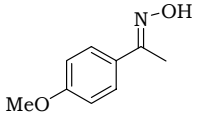


1-Phenyl-ethanone oxime (42): The oxime was obtained as a white solid in 95% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 10.09 (bs, 1H), 7.72-7.63 (m, 2H), 7.49-7.35 (m, 3H), 2.36 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =155.9, 136.4, 129.2, 128.5,

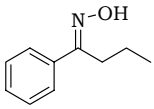
126.0, 12.4; **HRMS** calcd. for C_8H_9NO 135.068 found 135.069.



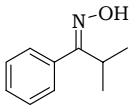
1-(4-Chloro-phenyl)-ethanone oxime (43): The oxime was obtained as a white solid in 94% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 9.42 (bs, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 2.33 (s, 3H), 2.25 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =155.7, 139.1, 133.5, 129.1, 125.8, 21.1, 12.2; **HRMS** calcd. for $C_9H_{11}NO$ 149.084 found 149.085.



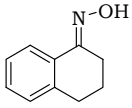
1-(4-Methoxy-phenyl)-ethanone oxime (44): The oxime was obtained as a white solid in 75% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 10.01 (bs, 1H), 7.60 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.30 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ =160.4, 155.3, 128.9, 127.3, 113.8, 55.2, 12.2; **HRMS** calcd. for $C_9H_{11}NO_2$ 165.079 found 165.081.



1-Phenyl-butan-1-one oxime (45): The oxime was obtained as a white solid in 95% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 8.92 (bs, 1H), 7.57-7.54 (m, 2H), 7.37-7.21 (m, 3H), 2.75 (t, *J* = 7.7 Hz, 2H), 1.63-1.47 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 159.4 (s), 135.8 (s), 129.0 (d), 128.4 (d), 126.2 (d), 28.1 (t), 19.7 (t), 14.2 (q); **HRMS** calcd. for $C_{10}H_{13}NO$ 163.100 found 163.105.



2-Methyl-1-phenyl-propan-1-one oxime (46): The oxime was obtained as a white solid in 79% yield as an 1:1 mixture of syn and anti isomers. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 9.19 (bs, 1H), 7.45-7.21 (m, 10H), 3.56 (m, 1H), 2.80 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 6H), 1.14 (d, *J* = 7.0 Hz, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 164.539, 162.9, 135.6, 133.6, 128.4, 128.3, 128.2, 128.0, 127.6, 127.4, 34.4, 27.6, 20.0, 19.2; **HRMS** calcd. for $C_{10}H_{13}NO$ 163.100 found 163.100.

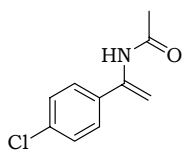


3,4-Dihydro-2*H*-naphthalen-1-one oxime (47): The oxime was obtained as a brown solid in 92% yield. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 10.0 (bs, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.29-7.19 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 2.86 (t, *J* = 6.5 Hz, 2H), 2.75 (t, *J* = 6.0 Hz, 2H), 1.86 (m, 2H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 155.2 (s), 139.8 (s), 130.3 (s), 129.2 (d), 128.6 (d), 126.4 (d), 123.9 (d), 29.7 (t), 23.9 (t), 21.2 (t); **HRMS** calcd. for $C_{10}H_{11}NO$ 161.084 found 161.086.

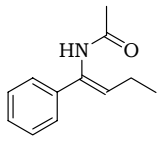
General procedure for the synthesis of enamides:

Method A: A mixture of 55.6 mmol of oxime, 12 ml (166 mmol) acetic anhydride, 6.2 g (111 mmol) Fe-powder (325 mesh) and 9.5 ml (166 mmol) acetic acid in 40 ml toluene was stirred for 4 h at 70°C. The mixture was cooled and filtered through Celite© and the residue was washed with toluene. The filtrates were washed with 2M $NaOH_{(aq)}$, dried over Na_2SO_4, filtered and concentrated. The crude enamides were purified by column chromatography and thoroughly washing with hexane.

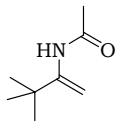
Method B: A mixture of 13.2 mmol oxime, 2.20 g (39.4 mmol) Fe-powder (325 mesh) and 0.95 ml (16.6 mmol) acetic anhydride in 100 ml DMF was stirred at RT for 6 h. The reaction was initiated by a few drops of TMSCl. The reaction mixture was diluted with water and extracted with 200 ml of ether. The organic layer was washed with water (2x 200 ml), brine (1x 200 ml), dried over Na_2SO_4, filtered and concentrated. The crude enamides were purified by column chromatography and thoroughly washing with hexane.



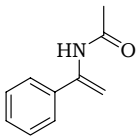
***N*-[1-(4-Chloro-phenyl)-vinyl]-acetamide (19)**: The enamide was obtained as a white solid in 17% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.32-7.28 (m, 5H), 5.71 (s, 1H), 5.07 (s, 1H), 2.06 (s, 3H) ;**^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 169.5 (s), 139.6 (s), 136.5 (s), 134.3 (s), 128.6 (d), 127.3 (d), 103.6 (t), 24.2 (q); **HRMS** calcd. for $C_{10}H_{10}ClNO$ 195.045 found 195.044.



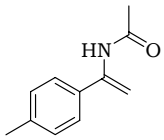
***N*-(1-Phenyl-but-1-enyl)-acetamide (20)**: The *Z*-isomer was isolated from a 3:2 mixture of *E*- and *Z*-isomers by column chromatography. (SiO_2, pentane / EtOAc, (4:1), R_f = 0.13). The *Z*-enamide was obtained as a white solid in a 3:1 mixture of rotamers in 21% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.41-7.19 (m, 5H), 7.10 (bs, 0.75H), 6.89 (bs, 0.25H), 5.93 (t, *J* = 7.2 Hz, 0.25H), 5.80 (t, *J* = 7.1 Hz, 0.75H), 2.31-2.09 (m, 2H), 2.08 (s, 2.25H), 1.76 (s, 0.75H), 1.11-1.01 (m, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.6, 168.7, 137.9, 134.1, 132.4, 129.3, 128.6, 128.4, 128.2, 128.1, 127.5, 125.4, 125.3, 23.1, 21.7, 21.2, 20.5, 13.4; **HRMS** calcd. for $C_{12}H_{15}NO$ 189.115 found 189.116.



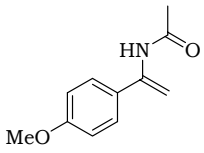
***N*-(2,2-Dimethyl-1-methylene-propyl)-acetamide (49)**: The enamide was obtained as colorless crystals in 36% yield. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 6.38 (bs, 1H), 5.61 (s, 1H), 4.79 (s, 1H), 2.08 (s, 3H), 1.11 (s, 9H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 168.8, 148.0, 98.9, 35.1, 28.1, 24.5; **HRMS** calcd. for $C_8H_{15}NO$ 141.115 found 141.115.



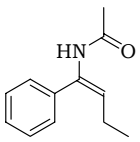
***N*-(1-Phenyl-vinyl)-acetamide (50)**: The enamide was obtained as a white solid in 17% yield. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 7.38 (m, 5H), 7.06 (bs, 1H), 5.83 (s, 1H), 5.08 (s, 1H), 2.08 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 169.5, 140.6, 138.0, 128.3, 125.9, 102.7, 24.0; **HRMS** calcd. for $C_{10}H_{11}NO$ 161.084 found 161.088.



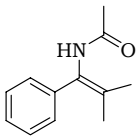
***N*-(1-*p*-Tolyl-vinyl)-acetamide (51)**: The enamide was obtained as a white solid in 44% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.99 (bs, 1H), 5.79 (s, 1H), 5.05 (s, 1H), 2.35 (s, 3H), 2.09 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 169.1 (s), 140.4 (s), 138.5 (s), 135.5 (s), 129.2 (d), 125.8 (d), 101.8 (t), 24.4 (q), 21.1 (q); **HRMS** calcd. for $C_{11}H_{13}NO$ 175.100 found 175.100.



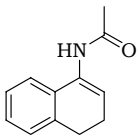
***N*-[1-(4-Methoxy-phenyl)-vinyl]-acetamide (52)**: The enamide was obtained as a yellow solid in 39% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.4 Hz, 2H), 7.12 (bs, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.69 (s, 1H), 4.99 (s, 1H), 3.79 (s, 3H), 2.06 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 169.1 (s), 159.8 (s), 140.1 (s), 130.8 (s), 127.2 (d), 113.8 (d), 101.4 (t), 55.2 (q), 24.3 (q); **HRMS** calcd. for $C_{11}H_{13}NO_2$ 191.095 found 191.096.



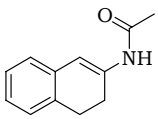
***N*-(1-Phenyl-but-1-enyl)-acetamide (53)**: The *E*-isomer was isolated from a 3:2 mixture of *E* and *Z* by column chromatography. (SiO_2, pentane / EtOAc, (4:1), R_f = 0.0.26). The *E*-enamide was obtained as a white solid in 28% yield. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.42 (bs, 1H), 7.34-7.23 (m, 5H), 6.11 (t, *J* = 7.8 Hz, 1H), 2.11-1.96 (m, 2H), 1.76 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 167.7, 135.5, 131.9, 127.1, 126.7, 126.3, 120.9, 22.4, 20.0, 13.3; **HRMS** calcd. for $C_{12}H_{15}NO$ 189.115 found 189.116.



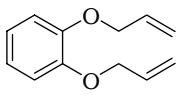
***N*-(2-Methyl-1-phenyl-propenyl)-acetamide (55)**: The enamide was obtained as a white solid in 42% yield as a 3:1 mixture of rotamers. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.30-7.14 (m, 5H), 6.91 (bs, 0.75H) 6.86 (bs, 0.25H), 1.94 (s, 2.25H), 1.81 (0.75H), 1.78 (s, 0.75H), 1.72 (s, 4.50H), 1.67 (s, 0.75H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.8 (s), 168.2(s), 138.7 (s), 130.0 (s), 129.0 (d), 128.1 (d), 127.8 (d), 127.4 (d), 127.0 (d), 23.1 (q), 21.1 (q), 21.0 (q), 20.6 (q); **HRMS** calcd. for $C_{12}H_{15}NO$ 189.115 found 189.116.



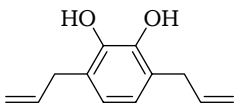
***N*-(3,4,4a,8a-Tetrahydro-naphthalen-1-yl)-acetamide (56)**: Mixture of rotamers (3:1); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.21-7.11 (m, 4H), 6.76 (bs, 0.75H), 6.65 (bs, 0.25H), 6.46 (bt, 0.75H), 5.97 (bt, 0.25H), 2.87-2.73 (m, 2H), 2.43-2.33 (m, 2H), 2.18 (s, 2.25H), 1.96 (s, 0.75H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 169.2 (s), 136.7 (s), 131.5 (s) 127.8 (d), 127.5 (d), 126.3 (d), 120.6 (d), 119.6 (d), 27.6 (t), 24.1 (q), 22.1 (t); **HRMS** calcd. for $C_{12}H_{13}NO$ 187.100 found 187.101.



***N*-(3,4,4a,8a-Tetrahydro-naphthalen-2-yl)-acetamide (58)**: A solution of 3.69 g (25.2 mmol) of *β*-tetralone, 7.45 g (126 mmol) acetamide and 0.96 g (5.04 mmol) *p*-toluenesulfonic acid in 150 ml toluene was refluxed under Dean-Stark conditions under an inert atmosphere for 20h. After cooling to RT, 250 ml of saturated $NaHCO_{3(aq)}$ was added, and the mixture was warmed to 60°C for 30 min. After cooling to RT, the organic layer was extracted and washed with water (3x 150 ml), dried over Na_2SO_4, filtered and concentrated. The enamide was purified by column chromatography (SiO_2, ether/pentane (1:2)). The enamide was obtained as a white solid, 3.74g (20.0 mmol; 80%); **^{1}H-NMR** (300 MHz, $CDCl_3$)[29] δ = 7.12-7.02 (m, 5H), 6.61 (bs, 1H), 2.89 (dd, *J* = 8.4 Hz, 7.7 Hz, 2H), 2.44 (dd, *J* = 8.4 Hz, 7.7 Hz, 2H), 2.12 (s, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$)[29] δ = 113.7, 100.2, 100.0, 99.2, 96.9, 96.8, 96.5, 96.4, 90.7, 57.4, 57.1, 56.0; **HRMS** calcd. for $C_{12}H_{13}NO$ 187.100 found 187.101.

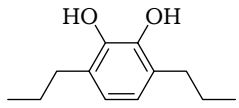


1,2-Bis-allyloxy-benzene (69): A solution of 22.0 g (0.20 mol) catechol **68**, 34.8 ml (0.40 mol) allylbromide and 60.8 g (0.45 mol) in 300 ml acetone was refluxed overnight. The reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with water, 5% $NaOH_{(aq)}$ and dried on Na_2SO_4. The solution was filtered and concentrated. The product was purified by distillation. Yield 33.1 g (0.17 mol; 85%). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.92 (s, 4H), 6.11 (ddt, *J* = 17.3 Hz, 10.5 Hz, 5.2 Hz, 2H), 5.44 (ddt, *J* = 10.5 Hz, 2.9 Hz, 1.5 Hz, 2H), 5.29 (ddt, *J* = 17.3 Hz, 3.3 Hz, 1.5 Hz, 2H), 4.62 (ddd, *J* = 5.2 Hz, 1.5 Hz, 1.5 Hz, 4H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 148.5, 133.4, 121.1, 117.4, 114.2, 69.8; **HRMS** calcd. for $C_{12}H_{14}O_2$ 190.099 found 190.100.

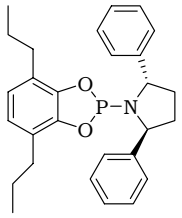


3,6-Diallyl-benzene-1,2-diol (70): 33.1 g (0.17 mol) of **69** was heated at 200°C for 4 h. The dark red reaction mixture was distilled. A yellow oil was obtained at 88-90°C and 0.3 mbar. The oil was purified by column chromatography (SiO_2; CH_2Cl_2) to obtain a yellowish oil, which solidified in a white solid after standing. Yield: 7.5 g (39.5 mmol; 23%) **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.70 (s, 2H), 6.13-5.99 (m, 2H), 5.60 (bs, 2H), 5.25-5.17 (m,

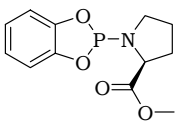
4H), 3.44-3.42 (m, 4H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 142.0, 136.5, 124.1, 121.4, 116.0, 34.6; **HRMS** calcd. for $C_{12}H_{14}O_2$ 190.099 found 190.101.



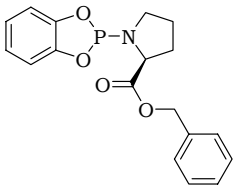
3,6-Dipropyl-benzene-1,2-diol (71): A mixture of 6.6 g (34.7 mmol) of **70** and 0.73 g 10% Pd/C in 70 ml of EtOH was stirred under H_2 (1 bar) for 2 d. The reaction mixture was filtered and the remaining solution was dried on Na_2SO_4 and concentrated to give a grey solid. Yield: 6.7 g (34.7 mmol: 100%). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.15 (bs, 2H), 2.50 (t, *J* = 7.7 Hz, 4H), 1.63-1.57 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 141.4, 126.2, 121.0, 31.7, 22.9, 14.0; **HRMS** calcd. for $C_{12}H_{18}O_2$ 194.131found 194.130.



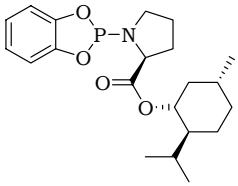
(*S*,*S*)-1-(4,7-Dipropyl-benzo[1,3,2]dioxaphosphol-2-yl)-2,5-diphenyl-pyrrolidine (L22): 0.93 g (4.80 mmol) of **71** was refluxed in 5 ml of PCl_3 overnight. The excess PCl_3 was removed by distillation. The resulting oil was dissolved in 5 ml of Et_2O and 0.65 ml (4.80 mmol) Et_3N. To the cooled solution (0°C) was added dropwise a solution of 1.07 g (4.80 mmol) **13** in 5 ml Et_2O. The mixture was stirred for 2h at RT. The suspension was filtered over Celite and the filtrate was concentrated. The remaining oil was purified by column chromatography. (Si_2O; pentane:EtOAc 10:1). The obtained solid was recrystallized to give colorless crystals. Yield 55 mg (0.12 mmol; 2.6%). **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.34-7.15 (m, 10H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 4.89 (d, *J* = 7.1 Hz, 2H), 2.82-2.60 (m, 2H), 2.39-2.23 (m, 2H), 1.86-1.51 (m, 6H), 1.31-1.13 (m, 2H), 1.07 (t, *J* = 7.3 Hz, 3H), 0.73 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 145.6, 145.5, 128.9, 128.1, 127.8, 126.7, 126.1, 124.6, 121.8, 121.2, 63.0, 62.9, 62.5, 52.5, 48.0, 33.4, 33.4, 32.0, 30.6, 23.2, 22.1, 18.6, 14.1, 13.9; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =143.2; **HRMS** calcd. for $C_{28}H_{32}NO_2P$ 445.217 found 445.216; **$[\alpha]_D^{20}$** = -29° (c= 0.43, $CHCl_3$).



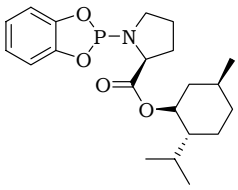
(*S*)-1-Benzo[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid methyl ester (L23): The ligand was obtained as a colorless sticky oil in 30% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.05-6.87 (m, 4H), 4.28-4.24 (m, 1H), 3.70 (s, 3H), 3.06-2.98 (m, 2H), 2.09-2.01 (m, 2H), 1.84-1.73 (m, 2H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 174.1, 145.9, 145.8, 121.8, 121.7, 111.3, 111.1, 59.4, 59.1, 52.3, 44.6, 44.5, 30.7, 30.6, 24.8; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =141.8; **HRMS** calcd. for $C_{12}H_{14}NO_4P$ 267.066 found 267.067; **$[\alpha]_D^{20}$** = -2° (c= 1.03, $CHCl_3$).



(*S*)-1-Benzo[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid benzyl ester (L24): The ligand was obtained as a colorless sticky oil in 60% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.42-7.33 (m, 5H), 7.05 (dd, *J* = 2.4 Hz, 6.8 Hz, 1H), 6.97-6.87 (m, 3H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.34-4.30 (m, 1H), 3.12-3.00 (m, 2H), 2.16-2.00 (m, 2H), 1.80-0.88 (m, 2H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.4, 146.0, 145.9, 145.8, 145.7, 135.4, 128.4, 128.2, 128.1, 121.8, 121.7, 111.2, 111.1, 66.9, 59.4, 59.2, 44.5, 44.4, 30.6, 30.5, 24.6; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =141.9; **HRMS** calcd. for $C_{18}H_{18}NO_4P$ 343.097 found 343.096; **$[\alpha]_D^{20}$** = -4° (c= 1.42, $CHCl_3$).



(*S,1R,2S,5R*)-1-Benzo[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (L25): The ligand was obtained as a colorless sticky oil in 36% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 6.97-6.94 (m, 1H), 6.92-6.89 (m, 1H), 6.84-6.80 (m, 2H), 4.62 (dt, *J* = 4.4 Hz. 10.6 Hz, 1H), 4.21-4.17 (m, 1H), 2.99-2.88 (m, 2H), 2.07-1.82 (m, 4H), 1.73-1.62 (m, 5H), 1.58-1.42 (m, 2H), 1.16-0.90 (m, 2H), 0.86 (dd, *J* = 4.4 Hz, 5.7 Hz, 6H), 0.70 (d, *J* = 7.0 Hz, 3H);**^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.2, 146.2, 146.1, 146.0, 145.9, 121.7, 121.6, 111.2, 111.1, 60.1, 59.8, 46.9, 44.2, 44.2, 40.6, 34.1, 31.3, 30.8, 30.7, 26.0, 24.7, 23.1, 21.9, 20.8, 15.9; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =142.5; **HRMS** calcd. for $C_{21}H_{30}NO_4P$ 391.191 found 391.192; **$[\alpha]_D^{20}$** = +54° (c= 0.98, $CHCl_3$).



(*S,1S,2R,5S*)1-Benzo[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (L26): The ligand was obtained as a colorless sticky oil in 47% yield. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.06-6.86 (m, 4H), 4.70 (dt, *J* = 4.4 Hz. 10.8 Hz, 1H), 4.28-4.24 (m, 1H), 3.01-2.90 (m, 2H), 2.09-1.85 (m, 3H), 1.84-1.67 (m, 6H), 1.51-1.40 (m, 2H), 1.26-0.95 (m, 2H), 0.91 (d, *J* = 6.2 Hz, 6H), 0.76 (d, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.2, 146.2, 146.1, 146.0, 145.9, 121.7, 121.6 111.2, 111.0, 60.0, 59.8, 46.8, 44.1, 40.6, 34.1, 31.3, 30.6, 30.6, 26.1, 24.6, 23.2, 22.0, 20.8, 16.1; **^{31}P-NMR** (81 MHz, $CDCl_3$) δ =142.7; **HRMS** calcd. for $C_{21}H_{30}NO_4P$ 391.191 found 391.192; **$[\alpha]_D^{20}$** = -25° (c= 0.99, $CHCl_3$).

General procedure for hydrogenations:

In a glass tube, 0.81 mg (2 µmol) of $Rh(COD)_2BF_4$, 4 µmol of ligand (2 µmol in case of the bidentate ligands **L8** and **L9**), 200 µmol of the substrate and 4 ml of solvent, was added. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) that was purged 4 times with nitrogen and once with hydrogen. Then, the autoclave was pressurized with 5 or 25 bar of hydrogen. The reaction mixture was stirred for 16 h. A sample of the resulting mixture was filtered over a silica plug and subjected to conversion (^{1}H-NMR) and e.e. determination (capillary GC). Full conversion was observed in most cases. As typical examples the isolated yields for **25**, **27**, **28** and **59** were determined. The complete reaction mixtures were filtered over a short silica plug (EtOAc) to yield the corresponding products in 99% yield. Absolute configurations were determined by comparison with reference compounds (**59**, **60**, **64**), literature values (GC or HPLC injections; **15**, **24**, **25**, **26**, **27**, **28**, **62**), optical rotation (**61**) or assigned by analogy through chiral GC elution order (**63**, **65**).

Table 2.6: *E.e.* determination for compounds **15**, **24**-**31**, **59**-**65** and **77**.

Entry	*Compound*	*Method*	*Retention time (min)*	*Retention time (min)*
1	**15**	A	6.7 (R)	7.1 (S)
2	**24**	B	12.8 (R)	14.9 (S)
3	**25**	C	3.4 (R)	3.9 (S)
4	**26**	D	11.5 (S)	11.7 (R)
5	**27**	E	15.8 (S)	16.7 (R)
6	**28**	F	39.4 (S)	41.0 (R)
7	**29**	K	11.6 (R)	14.1 (S)
8	**30**	B	6.9[a]	8.1[a]
9	**31**	L	10.9 (R)	13.6 (S)
10	**59**	G	12.8 (S)	13.9 (R)
11	**60**	H	15.8 (S)	16.7 (R)
12	**61**	H	13.5 (S)	14.6 (R)
13	**62**	E	9.0 (S)	9.5 (R)
14	**63**	I	12.1 (S)	12.7 (R)
15	**64**	E	14.0 (S)	15.4 (R)
16	**65**	E	17.0 (S)	17.6 (R)
17	**77**	J	13.0 (S)	13.9 (R)

a) Absolute configuration is not known

Method A: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12µm), 160°C
Method B: Chiralcel-OD (0.46 cm x 25 cm), *i*-PrOH: heptane 1:9
Method C: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12µm), 110°C

Method D: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 160°C
Method E: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 170°C
Method F: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 130°C
Method G: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 100°C
Method H: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 140°C
Method I: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 150°C
Method J: CP Chiraldex G-TA from Altrack (30m x 0.25 mm x 0.125 μm), 80°C
Method K: Chiralcel-OD (0.46 cm x 25 cm), *i*-PrOH: heptane 5:95
Method L: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12μm), 100°C

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Chapter 3
PegPhos; a Water-soluble Phosphoramidite

In this chapter, the results of a study on the rhodium-catalyzed asymmetric hydrogenation of N-acyl dehydroalanine with a chiral water-soluble monodentate phosphoramidite ligand are described. Enantioselectivities up to 89% have been achieved.

Part of this chapter has been published:

Hoen, R.; Leleu, S.; Botman, P. N.; Appelman, V. A. M.; Feringa, B. L.; Hiemstra, H.; Minnaard, A. J.; Maarseveen, J. H. *Org. Biomol. Chem.* **2006**, *4*, 613-615.

3.1 Introduction

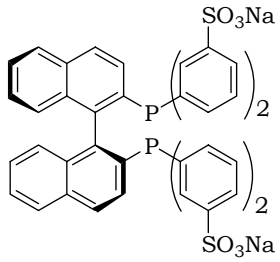
3.1.1 Organic synthesis in water

Water is a very attractive solvent for organic synthesis from an economical as well as an environmental point of view.[1] Extensive research has been done on the use of water as solvent for (stereoselective) organic reactions, such as Diels-Alder reactions, oxidations and reductions, Claisen rearrangements, and aldol condensations. Also the field of transition metal catalyzed reactions, applying water as a solvent, has been studied extensively. Examples of these reactions are: cross-coupling reactions, Diels Alder reactions, Heck reactions, carbonylations, hydroformylations and hydrogenations.

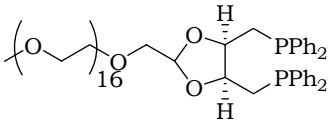
3.1.2 Hydrogenations in water

Although hydrogenation reactions in water are well documented,[2] only a limited number of reports have appeared describing asymmetric hydrogenations in an aqueous environment. In general, the low water solubility of many catalysts and substrates causes a decrease in reaction rate. The obvious way to avoid this problem is to make these ligands water-soluble. In most cases, chiral ligands used for these reactions are water-soluble analogues of well-known bidentate phosphines (*e.g.* BINAP, DIOP, BDPP and BIFAP)[3] as well as ligands based on carbohydrates[4] or amino acids (Figure 3.1).[5]

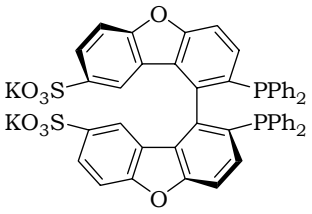
The use of biphasic systems makes it possible to recycle these water soluble ligands.[6] In a series of articles, Sinou and co-workers report the use of sulphonated phosphines in a mixed solvent system of water and ethylacetate.[7] The product and the catalyst could be obtained separately by a simple phase-separation. The aqueous phase, containing the catalyst, could be reused. Uemera *et al.* applied the same strategy as described before, using a water-soluble catalyst based on sugar derivatives.[4d,e] They could reuse their catalyst several times without any lost of activity and selectivity.



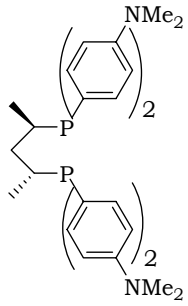
BINAP-4SO_3Na (**L1**)[3a,b]



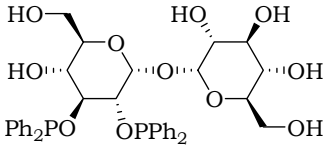
PegDIOP (**L2**)[3c]



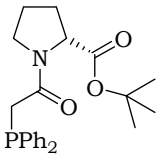
(*S*)-(-)-BIFAPS (**L3**)[3e]



BDPP-4NMe_2 (**L4**)[3d]



α,α-trehalose
derived diphosphite (**L5**)[4]



proline
derived phosphine (**L6**)[5]

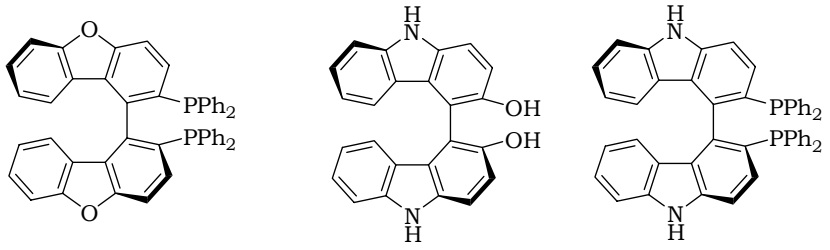
Figure 3.1: Water-soluble phosphorus ligands.

An alternative method to increase the efficiency of catalysts in aqueous media is by adding surfactants. In 1992, Oehme and co-workers reported that the asymmetric hydrogenation of a variety of α-dehydroamino acids in aqueous media could be promoted by the addition of surfactants.[8] In the following years, a variety of surfactants were introduced by Oehme and Selke for the rhodium-catalyzed asymmetric hydrogenation of different substrates.[9] Whereas the increase of reaction rates is a concentration effect, the reason for the increase in enantioselectivity is still not fully understood.[9n,o] Concentration of the substrate and catalyst in a hydrophobic surrounding might be an explanation, although there is a range of factors which play a role, *e.g.* solubility of substrate, cmc,[10] structure of amphiphile, structure of catalyst, etc.

3.1.3 BICOL

The number of C_2-symmetric biaryl ligands for transition metal catalyzed reactions has steadily increased since the introduction of BINAP by Noyori in the early 80's.[11] Most of these ligands are based on BINOL,[12] although other backbones have been used as well, for example DuPhos,[13] SpiroPhos[14] or the TunaPhos family of ligands of Zhang and co-workers.[15]

Modification in the BINOL backbone is still a tedious and time-consuming work. An alternative for the BINOL backbone was developed by Hiemstra and co-workers *e.g.,* the dibenzofuran-based diphosphine BIFAP (**L7**) (Figure 3.2).[3e] Advantage of the dibenzofuran backbone is the high regioselectivity in the sulphonation of BIFAP (**L7**) to obtain its water-soluble equivalent BIFAPS (**L3**) (Figure 3.1). The two ligands showed excellent results in the asymmetric Ru-catalyzed hydrogenation of several substrates in both organic solvents and in aqueous media.[3e] The nitrogen analogue of BIFAP (**L7**), BICAP (**L8**) (Figure 3.2) showed excellent results in the asymmetric hydrogenation of methyl acetoacetate and dimethyl itaconate.[16, 17] The presence of the amine functionality in the backbone makes it easy to substitute the BICOL, which is the precursor of BICAP (**L8**), in order to fine-tune the electronic and steric properties of the ligand.



(*S*)-BIFAP (**L7**) (*S*)-BICOL (**7**) (*S*)-BICAP (**L8**)

Figure 3.2: BINOL analogues.

3.1.4 Goal of this research

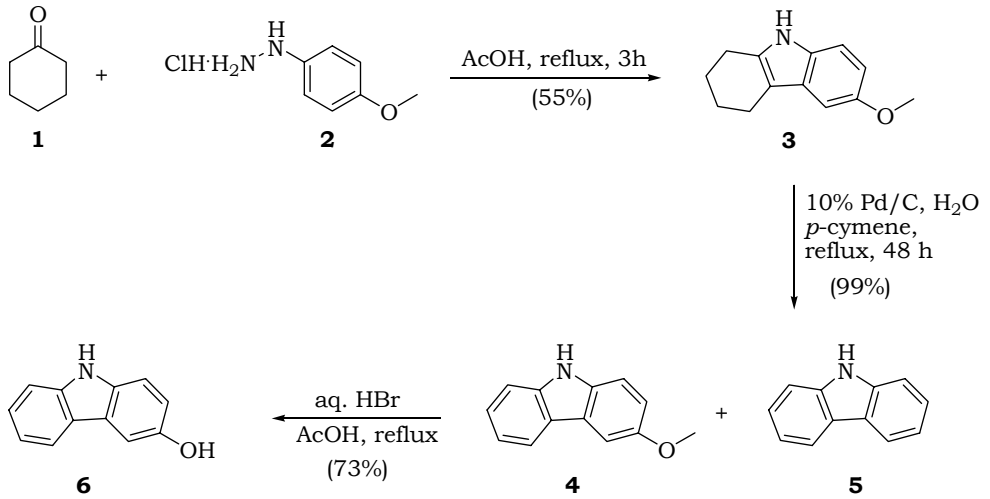
The goal of this research is the design and synthesis of a water-soluble monodentate phosphoramidite, and application of this as a ligand in rhodium-catalyzed hydrogenation. It was decided to use BICOL (**7**) as a backbone due to the possibility of easy modification. To increase the solubility of the ligand in water, BICOL (**7**) was equipped with polyethylene glycol chains.

The project is a co-operation between the groups of Van Maarseveen / Hiemstra and Minnaard / Feringa. The synthesis described in the following paragraphs has been performed by Dr. Stephane Leleu and Drs. Vanessa A. M. Appelman.

3.2 Synthesis of PegPhos

3.2.1 Synthesis of 3-hydroxycarbazole

The synthesis of BICOL (**7**) has been carried out according to a route developed by Hiemstra *et al.*[17] (Scheme 3.1).

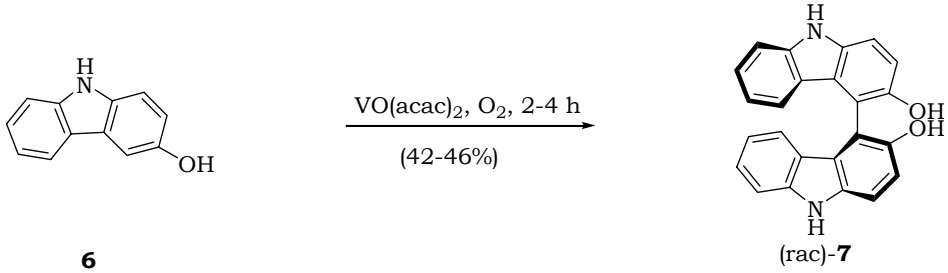


Scheme 3.1: Synthesis of 3-hydroxycarbazole **6**.

The initial tetrahydrocarbazole **3** was synthesized by a method developed by Rogers and Corson.[18] The Fisher indole reaction of cyclohexanone (**1**) and *p*-methoxyphenylhydrazine (**2**) proceeded smoothly and gave the tetrahydrocarbazole **3** in a moderate yield. Dehydrogenation of **3** on 10% Pd/C, deactivated by water, gave **4** in almost quantitative yield. Deactivation of the catalyst appeared to be essential. The yield of demethoxylated side-product **5** was much higher when the catalyst was not deactivated. Use of the deactivated catalyst gave only traces (≈1%) of the unwanted side-product. Deprotection of the methoxy group by 48% $HBr_{(aq)}$ in acetic acid yielded 3-hydroxycarbazole (**6**) in good yield.

3.2.2 Oxidative coupling

The key step in the synthesis of BICOL (**7**) is the oxidative dimerization of 3-hydroxycarbazole (**6**) (Scheme 3.2). It was chosen to perform the reaction with $VO(acac)_2$ as a catalyst, although other catalysts gave similar results.[17] The reaction was monitored by TLC and stopped after complete disappearance of the starting material. Immediate removal of the catalyst by filtration after completion appeared to be necessary to avoid overoxidation of the diol to, probably, quinone-like products. The reaction could be performed on a 2 g scale. Attempts to perform the reaction on a larger scale gave lower yields.



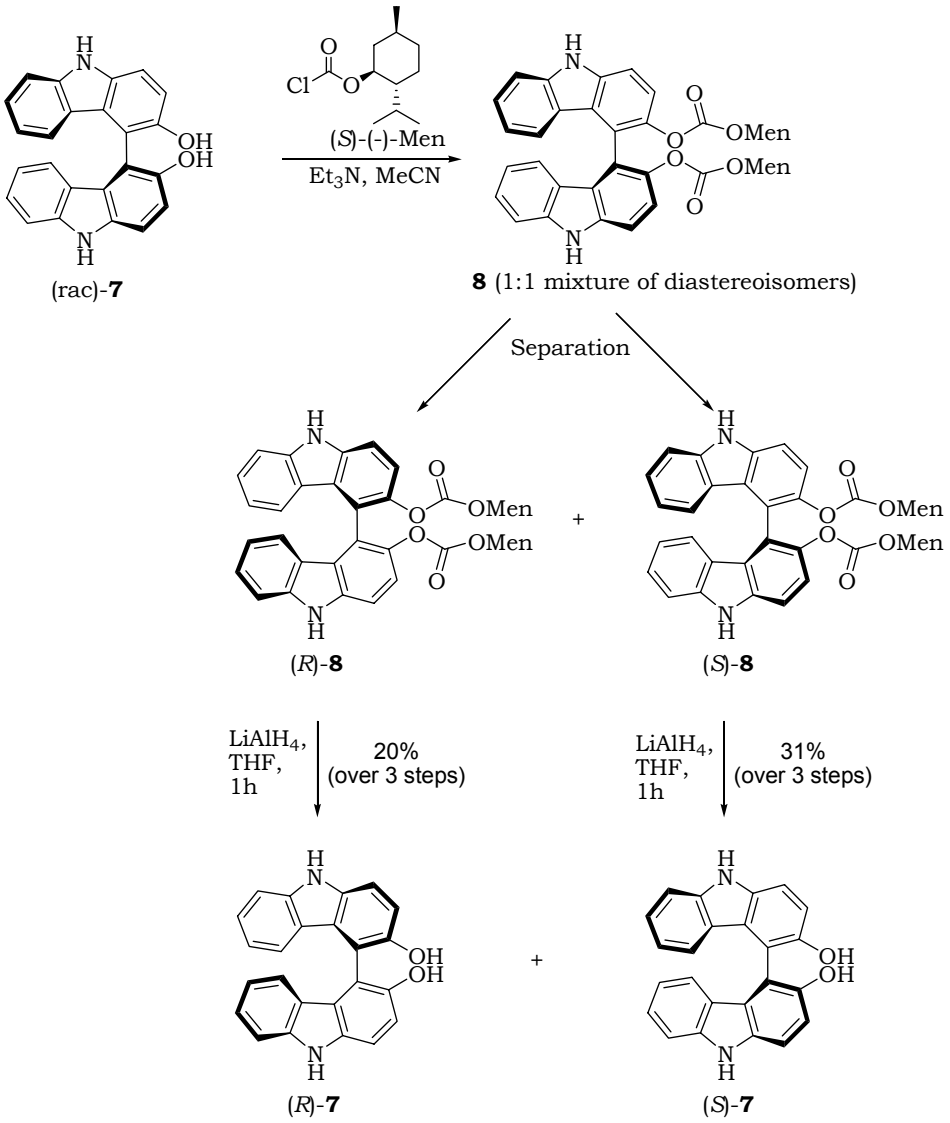
6 (rac)-**7**

Scheme 3.2: Oxidative coupling of 3-hydroxycarbazole (**6**).

3.2.3 Resolution of (±)-BICOL

Resolution of the enantiomers of (±)-BICOL (**7**) was done using (*R*) or (*S*)-menthyl chloroformate as resolving agent (Scheme 3.3). Reaction of **7** with

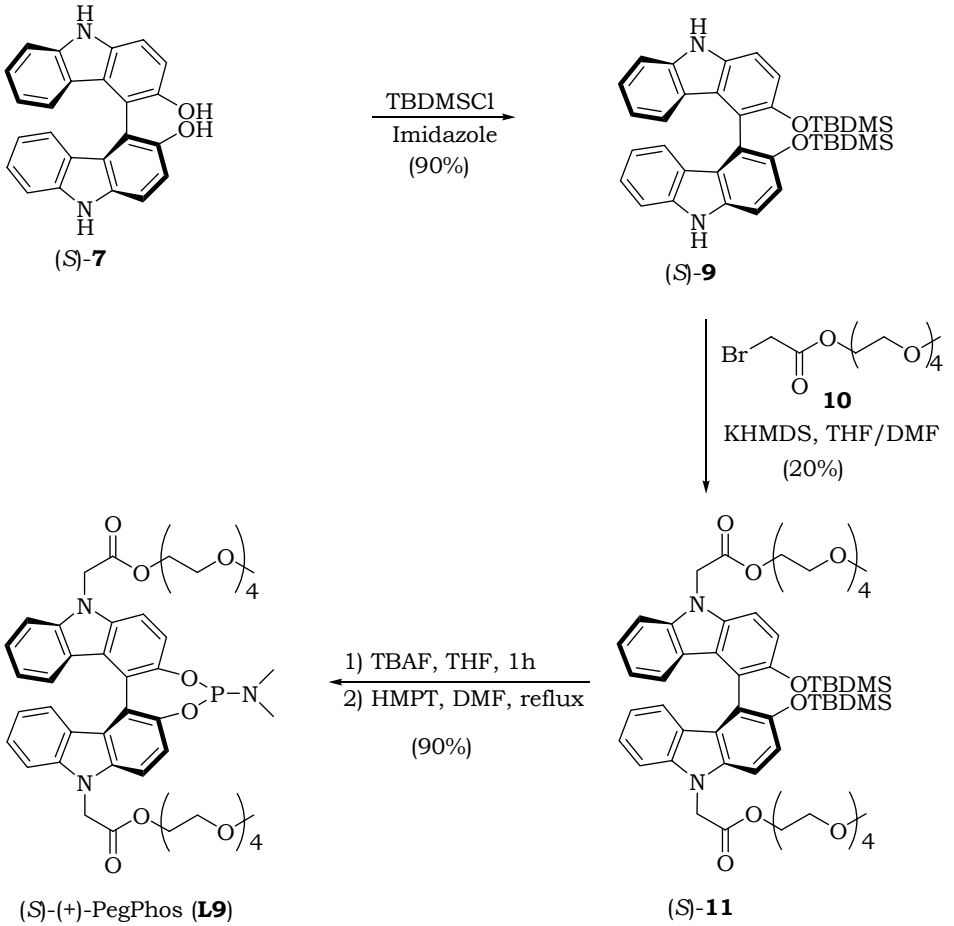
(*R*)-menthyl chloroformate gave diastereomers **8**, which could be separated by column chromatography. Removal of the resolving agents by reduction with $LiAlH_4$, gave enantiomerically pure (+)- and (-)-BICOL (**7**).



Scheme 3.3: Resolution of (±)-BICOL (**7**).

3.2.4 Synthesis of PegPhos

(*S*)-(+)-PegPhos (**L9**) could be synthesized in three steps starting from (*S*)-(-)-BICOL (**7**) (Scheme 3.4).

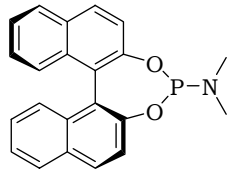


Scheme 3.4: Synthesis of (*S*)-(+)-PegPhos (**L9**).

Protection of the hydroxy groups with TBDMSCl proceeded smoothly and (S)-**9** was obtained in 90% yield. Alkylation of (S)-**9** with bromoacetic acid derivative **10**[19] was troublesome. Product **11** was obtained in a poor yield of 20%. Deprotecting of the TBDMS diether by TBAF and subsequently reaction of the dihydroxy compound (not shown) with HMPT gave the monodentate phosphoramidite **L9** in 77% yield over two steps.

The ^{31}P-NMR showed a single peak at 148 ppm, which is typically for phosphoramidites.[20] Furthermore, no traces of amines were detected in the ^{1}H- and ^{13}C-NMR spectra. Also the characteristic IR-absorption of the carbonyl was observed at 1750 cm^{-1}.

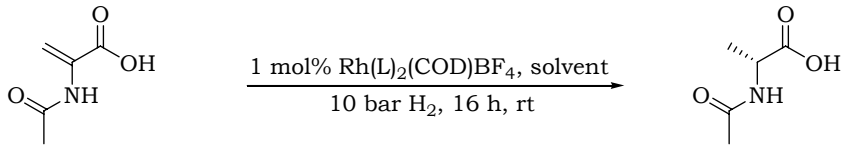
3.3 Hydrogenations with PegPhos



MonoPhos (**L10**)

The catalytic performance of PegPhos (**L9**) as a ligand was compared with MonoPhos which has proven to be highly effective in the asymmetric hydrogenation of dehydroamino acids.[21] The catalyst was obtained by reaction of two equivalents of the ligand with $Rh(COD)_2BF_4$ in CH_2Cl_2 and subsequent removal of the solvent. *N*-acyl dehydroalanine (**12**) was chosen as a representative and reasonably water-soluble substrate,. The hydrogenation reactions were performed in a semi-automated eight reactors Endeavor™ autoclave pressurized with 10 bar of hydrogen. The results are depicted in Table 3.1.

Table 3.1: Hydrogenation of *N*-acyl dehydroalanine (**12**).



12 **13**

Entry	*Conditions*	*PegPhos*		*MonoPhos*[c]	
		E.e.[a,b]	*T.O.F.*	*E.e.*[a,b]	*T.O.F.*
1	DCM	57	133	90 (82)	400 (133)
2	MeOH	90	1200	95 (94)	600 (600)
3	MeOH / H_2O	89	1200	65 (54)	20 (55)
4	H_2O	82	55	16 (0)	20 (25)
5	MeOH + 10% SDS	74	2000	89 (83)	63 (300)
6	MeOH / H_2O + 10% SDS	82	750	80 (47)	20 (92)
7	H_2O + 10% SDS	89	600	83 (79)	50 (44)

(a) *E.e's* in % obtained by chiral GC (b) Products were analyzed as their corresponding methyl esters (c) Between brackets the results of *in situ* formed catalyst.

Initial experiments in CH_2Cl_2 with 1 mol% of catalyst gave full conversion and *e.e.'s* of 57% and 90% for PegPhos (**L9**) and MonoPhos (**L10**), respectively, both in favor of the *R*-product and with T.O.F.'s of 133 h^{-1} and 400 h^{-1} (entry 1). By switching to the more polar solvent MeOH, especially PegPhos (**L9**) showed a remarkable 9-fold reaction rate increase and also the *e.e.* now reached 90% (entry 2). The addition of water slowed down the activity of MonoPhos (**L10**) drastically (30-fold) together with a significant drop in *e.e.*, in sharp contrast with PegPhos (**L9**) that fully maintained its high rate and enantioselectivity (entry 3). In pure water PegPhos (**L9**) still gave a respectable 82% *e.e.* but at the expense of a 22-fold rate decrease while under the same conditions MonoPhos (**L10**) almost lost most of its enantioselectivity and activity (entry 4). These results show that the phosphoramidite moiety is compatible with water, which has been observed before in for example Rh-catalyzed boronic acid additions.[22]

The addition of surfactants is known to influence the activity and selectivity of homogeneous catalysts in highly polar solvents (*vide supra*). Regarding the *e.e.*, no beneficial effect could be seen after addition of SDS* to MeOH (entry 5) or a water/MeOH mixture (entry 6). By adding SDS to water, the *e.e.* obtained with MonoPhos (**L10**) increased from 16% to 83% together with a more than 2-fold increase of the T.O.F. Under these conditions PegPhos (**L9**) clearly outperformed MonoPhos by reaching an *e.e.* of 89% as well as a 12-fold higher rate.

3.4 Conclusion

It has been shown that the versatile biscarbazole-based BICOL skeleton can be functionalized with polyethylene glycol units at the nitrogen atoms to render this highly apolar moiety soluble in water. The resulting PegPhos was superior to the parent MonoPhos (**L10**) ligand, in activity as well as in selectivity, in the enantioselective Rh-catalyzed hydrogenation of *N*-acyl dehydroalanine (**12**) in polar solvents, especially in water. Whereas there are a number of *bidentate* phosphine ligands which give better enantioselectivities (> 99%)[23] in the hydrogenation of dehydroamino acids,[1-4] to the best of our knowledge, this is the first *monodentate* ligand

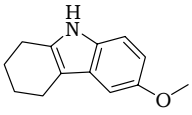
* SDS = Sodium Dodecyl Sulphate

providing high *e.e.'s* in the Rh-catalyzed enantioselective hydrogenation of *N*-acyl dehydroalanine (**12**) in water.

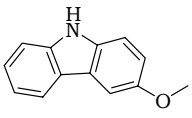
3.5 Experimental section

General Remarks:

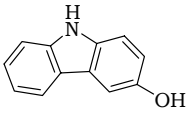
Unless noted otherwise, chemicals were purchased from commercial suppliers and used without purification. DMF was distilled from KOH and stored over mol sieves (4Å). CH_2Cl_2 was freshly distilled from calcium hydride. THF, toluene and diethyl ether were freshly distilled from sodium and benzophenone as indicator. MeCN was dried over Na_2SO_4. Et_3N was stored over KOH pallets. PE 60-80 was freshly distilled. All reactions were performed under inert atmosphere and using flame dried glassware. Column chromatography was performed using silica gel (Aldrich 70-230 mesh, 60 Å). R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}). ^{1}H- and ^{13}C-NMR spectra were determined with a Bruker ARX 400 (400 and 100.6 MHz respectively). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. ^{31}P nuclear magnetic resonance spectra were determined with a Varian Mercury-VX (121.5 MHz). Chemical shifts (δ) are given in ppm downfield from 85% H_3PO_4. Coupling constants (*J*) are given in Hertz. IR spectra were obtained from NaCl plates using a Perkin-Elmer 1310 spectrophotometer and wavelengths (ν) are in cm^{-1}.



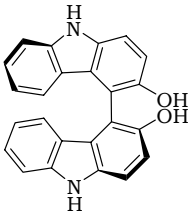
2-Methoxy-6,7,8,9-tetrahydrocarbazole (3): To a mixture of 90.2 g (0.92 mol) of freshly distilled cyclohexanone (**1**) and 330 ml of acetic acid was added in portions 100 g (0.92 mol) of *p*-methoxyphenylhydrazine (**2**) at room temperature. After refluxing for 3 h, the mixture was cooled to 0°C for 5 h. The mixture was filtered to obtain a brown powder. The product was obtained in 55% yield after recrystallization from a 5:1 mixture of water/ethanol. Spectroscopic data were according to the literature values.[24]



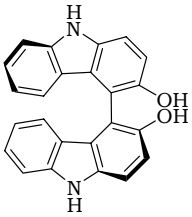
2-Methoxycarbazole (4): To a solution of 1 g (4.96 mmol) of **3** in 10 ml of *p*-cymene and 2 ml of water, was added 0.5 g of 10 % Pd on carbon. The resulting suspension was refluxed for 48 h, cooled to room temperature and filtered. The residue was washed with boiling ethyl acetate. The collected filtrates were concentrated *in vacuo* to yield a 99:1 mixture of **4** and **5**. (0.96 g; 4.95 mmol; 99 %). Spectroscopic data were according to the literature values.[25]



2-Hydroxycarbazole (6): To a solution of 30 g (0.15 mol) of **4** in 140 ml of AcOH was added a solution of 138.5 ml, (1.21 mol) of 48 % $HBr_{(aq)}$. After 2 h refluxing the mixture was cooled to 0°C. The product precipitated and was collected by filtration. The product was obtained as grey crystals. (20.4 g; 0.11 mol; 73 %) Spectroscopic data were according the literature values.[26]



(Rac)-(9H,9'H-[4,4']-Bicarbazolyl-3,3'-diol (BICOL) (7): To a solution of 2 g (10.8 mmol) of 3-hydroxycarbazole (**6**) in 80 ml of acetonitrile was added 140 mg (0.5 mmol) of $VO(acac)_2$. The solution was stirred at room temperature while the progress of the reaction was monitored by TLC. The reaction was immediately stopped by filtration on celite/silica gel (80/20) after disappearing of the starting material. The residue was washed with 50 ml of acetonitrile. The solution was concentrated *in vacuo*. The obtained dark solid was purified by column chromatography (PE/EtOAc, 80/20 → 60/40) affording 0.91 g (2.50 mmol; 46%) of **7** as a brown powder. **M.p.** 327-328°C; $\mathbf{R_f}$ = 0.24; **^{1}H-NMR** ($CDCl_3$): δ = 10.14 (bs, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.12 (m, 4H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.56 (dt, *J* = 7.2, 0.9 Hz, 2H; **^{13}C-NMR** ($CDCl_3$): δ = 147.9, 140.4, 134.1, 124.4, 123.0, 122.0, 121.1, 117.2, 116.6, 114.9, 110.3, 110.1.



Resolution of BICOL (7): To a stirred solution of 10 g (27.5 mmol) of racemic BICOL **7** and 19.1 ml of triethylamine in 250 ml of acetonitrile was added dropwise 13.6 ml (63 mmol) of (-)-(1*R*)-menthyl chloroformate. The solution was stirred for 1 h at room temperature. The reaction was quenched by addition of 300 ml of ethyl acetate and 100 ml of water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 150 ml). The combined organic layers were dried over Mg_2SO_4, filtered and concentrated under reduced pressure.

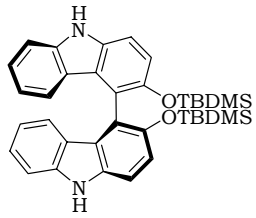
Purification and separation of diastereomers by chromatography (PE/CH_2Cl_2, 80/20 → 40/60 → CH_2Cl_2) afforded 3 fractions : the first fraction was the diastereomer (-)-(*aS*)-**8** (2.40 g, 12 % out of maximum 50%), the second fraction was a mixture of (-)-(*aS*)-**8** and (-)-(*aR*)-**8** in 3:1 ratio (7.20 g) and the third fraction was the diastereomer (-)-(*aR*)-**8** (6.80 g, 34 % out of maximum 50%).

The third fraction was recrystallized from refluxing diisopropyl ether yielding 6.2 g (8.52 mmol; 31% out of maximum 50%) of (-)-(*aR*)-**8** as a white solid.

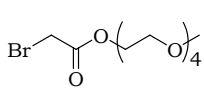
The first and the second fraction (9.60g, 13.2 mmol) were dissolved in 250 ml of THF. To this solution was added 5.1 g (96 mmol) of $LiAlH_4$ in 4

portions over 10 min. The reaction mixture was stirred for an additional 1 h at room temperature. The reaction was carefully quenched by adding water, ethyl acetate and 1M aqueous HCl. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE/EtOAc, 1:1) afforded a mixture of (*S*)-BICOL and (*R*)-BICOL as a white solid (3.08 g, 8.46 mmol, 64%). This mixture was reacted with (+)-(1*S*)-menthylchloroformate according to the procedure described above, yielding a mixture of (+)-(a*S*)-**8** and (+)-(a*R*)-**8**. Purification and separation of the diastereomers was done by column chromatography (PE/CH_2Cl_2, 80/20 → 40/60 → CH_2Cl_2). The second fraction recrystallized from diisopropyl ether yielding 4.41g (6.06 mmol; 72% out of maximum 75%) of (+)-(*aS*)-**8** as a white solid.

Both diastereomerically pure (-)-(*aR*)-**8** and (+)-(*aS*)-**8** were treated with $LiAlH_4$ according to the procedure described above, yielding enantiomerically pure (*R*)-(+)- and (*S*)-(-)-BICOL, respectively, in 65 % yield after purification by chromatography (PE/EtOAc, 50/50). Spectroscopic data were according the literature values.[17]

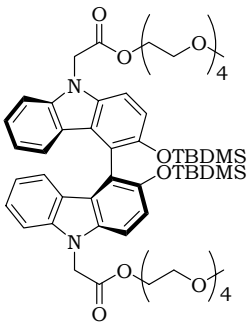


(*S*)- 3,3'-Bis-(tert-butyl-dimethyl-silanyloxy)-9H,9'H-[4,4']-bicarbazolyl (9): A solution of 0.5 g (1.37 mmol) of BICOL **7**, 0.33 g (4.80 mmol) of imidazole and 0.54 g (3.57 mmol) of TBDMSCl in 14 ml of MeCN was heated at 65 °C for 4 h. After cooling to room temperature the reaction was quenched with H_2O, EtOAc and $NaHSO_4$. The product was extracted with EtOAc and the water layer was extracted twice with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc, 60/40) afforded 0.69 g (1.23 mmol; 90%) of **9** as an off-white foam. R_f = 0.57. **^{1}H-NMR** ($CDCl_3$): δ = 7.93 (s, 2 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 7.2 Hz, 2 H), 7.18 (t, *J* = 7.2 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.69 (t, *J* = 7.2 Hz, 2 H), 0.5 (s, 18 H), -0.01 (s, 6 H), -0.20 (s, 6 H); **^{13}C-NMR** ($CDCl_3$): δ = 146.8, 140.2, 134.5, 124.9, 123.9, 123.5, 122.3, 121.7, 118.4, 117.4, 109.6, 109.5, 25.0, 17.5, -4.7, -4.9; **IR** (NaCl, cm^{-1}) 3422, 2954, 2929, 2886, 2856, 1507, 1478, 1435, 1287, 1265, 952, 832.

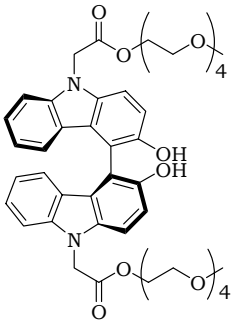


Bromo- acetic acid 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester (10): To a stirred solution of 2.58 g (18.5 mmol) of bromoacetic acid and 1.9 ml (22.2 mmol) of $SOCl_2$ in 185 ml of CH_2Cl_2, was added dropwise 5.0 g (24 mmol) tetraethylene glycol monomethylether and the resulting reaction mixture was stirred at room temperature overnight. The solvent was removed

under reduced pressure and the product was purified using column chromatography on silica gel (eluens PE/EtOAc, 1:3) yielding 4.98 g (15.6 mmol, 82%) of a yellow liquid. $\mathbf{R_f}$-value: 0.15 (PE/EtOAc, 50/50); **^{1}H-NMR** ($CDCl_3$): δ = 4.31 (t, *J* = 4.7 Hz, 2H), 3.85 (s, 2H), 3.71 (t, *J* = 4.8 Hz, 2H), 3.64 (m, 10H), 3.53 (t, *J* = 4.9 Hz, 2H), 3.36 (s, 3H); **^{13}C-NMR** ($CDCl_3$): δ = 166.95, 71.64, 70.35, 70.32, 70.31, 70.28, 70.21, 68.45, 65.03, 58.72, 25.62; **IR** (NaCl, cm^{-1}) : 1736.5.

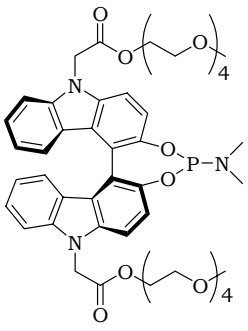


(*S*)-*N*-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester-3,3'-bis-(tert-butyl-dimethyl-silanyloxy)-9H,9'H-[4,4']-bicarbazole (11): To a solution of 722 mg (1.22 mmol) of **9** in 12.2 ml of THF and 12.2 ml of DMF, was added dropwise 6.4 ml (2.81 mmol) of KHMDS at 0ºC and the solution was stirred at room temperature for 1 h. Next 1.9 g (4.88 mmol) of **10** was added dropwise and the resulting reaction mixture was stirred at room temperature for 4 h. After this time a two-phase separation was carried out using EtOAc, water, brine and NH_4Cl. The organic phase was washed 4 times with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was further purified using column chromatography on silica gel (PE/EtOAc, 4/1 – 0/1/5% MeOH) yielding 260 mg (0.24 mmol; 20%) of a brown oil. $\mathbf{R_f}$-value: 0.24 (EtOAc); **^{1}H-NMR** ($CDCl_3$): δ = 7.26 (d, *J* = 4.0 Hz, 2H), 7.13 (d, *J* = 3.6 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.64 (m, 2H), 5.01 (s, 4H), 4.24 (m, 4H), 3.58 (m, 24H), 3.47 (m, 4H), 3.29 (d, *J* = 6.8 Hz, 6H), 0.38 (s, 18H), -0.11 (s, 6H), -0.31 (s, 6H); **^{13}C-NMR** ($CDCl_3$): δ = 168.63, 147.16, 141.10, 135.70, 125.20, 123.64, 123.24, 122.52, 121.90, 118.76, 117.41, 107.43, 76.68, 70.56, 68.77, 65.29, 64.43, 61.01, 58.98, 44.75, 30.88, 25.78, 25.06, 17.56, -4.60; **IR** (NaCl, cm^{-1}) : 1754 ; **$[\alpha]_D^{20}$** (*S*)-**11** = - 77° (c = 0.55, $CHCl_3$).



(*S*)-*N*-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester- 9H,9'H-[4,4']-bicarbazole-3,3'-diol (14): To a solution of 260 mg (0.23 mmol) of **11** in 5 ml of THF, was added 0.48 ml (0.47 mmol) of TBAF. The resulting reaction mixture was stirred at room temperature for 10 min. After this time a two-phase separation was carried out using EtOAc, water, brine and 0.5 M $NaHSO_3$. The organic phase was washed once with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was further purified using column chromatography on silica gel (PE/EtOAc, 0/1) yielding 169 mg (0.20 mmol; 85%) of a brown oil (169 mg, 85 %). $\mathbf{R_f}$-value: 0.06 (EtOAc); **^{1}H-NMR**

($CDCl_3$): δ = 7.40 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.20 (m, 4H), 6.76 (d, *J* = 7.8 Hz, 2H), 6.71 (m, 2H), 5.03 (s, 4H), 4.27 (m, 4H), 3.57 (m, 18H), 3.47 (m, 10H), 3.28 (s, 6H); **^{13}C-NMR** ($CDCl_3$): δ = 168.47, 148.32, 141.00, 135.50, 125.61, 122.48, 121.92, 121.56, 119.14, 115.17, 113.46, 109.67, 107.87, 71.65, 70.23, 68.57, 64.63, 60.19, 58.73, 53.58, 44.59, 29.03, 13.99; **IR** (NaCl, cm^{-1}) : 3333, 1750 ; **$[\alpha]_D^{20}$** (*S*)-**15** = - 45° (c = 0.5, $CHCl_3$).



(*S*)-*N*-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester- 9H,9'H-[4,4']-Bicarbazole-3,3'-O_2PNMe_2 (L9): To a solution of 169 mg (0.19 mmol) of **15** in 2 ml of MeCN, was added 37 µl (0.19 mmol) of HMPT and the resulting reaction mixture was refluxed at 70 °C for 4 h. After this time the solvent was removed under reduced pressure to obtain 160 mg (0.17 mmol; 90%) of a yellow oil. **R_f**-value: 0.04 (EtOAc); **^{31}P-NMR** ($CDCl_3$): δ = 148.05; **^{1}H-NMR** ($CDCl_3$): δ = 7.47 (d, *J* = 1.6 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.24 (m, 4H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.51 (m, 2H), 5.14 (m, 4H), 4.34 (m, 4H), 3.63 (m, 4H), 3.54 (m, 20H), 3.49 (m, 4H), 3.35 (d, *J* = 1.2 Hz, 12H), 2.55 (d, *J* = 8.9 Hz, 6H); **^{13}C-NMR** ($CDCl_3$): δ = 168.24, 168.20, 144.87, 144.75, 140.99, 140.94, 137.68, 137.13, 125.65, 122.63, 122.50, 122.43, 122.21, 119.63, 118.80, 118.76, 108.85, 108.75, 107.63, 107.57, 71.72, 70.39, 70.32, 70.29, 68.64, 68.61, 64.57, 64.48, 58.82, 44.60, 35.93, 35.72 ; **IR** (NaCl, cm^{-1}) : 1751 ; **$[\alpha]^{20}_D$** (*S*)-**12** = + 297° (c = 0.1, CH_3Cl).

Preparation of the catalysts:

The Rh complex was prepared *in situ* by dissolving 0.083 mmol of $Rh(COD)_2BF_4$ and 0.17 mmol of the appropriate ligand in 3.2 ml of CH_2Cl_2. The yellow solution was stirred for 30 min and subsequently concentrated under reduced pressure, yielding a yellow powder which was used without purification.

General procedure for hydrogenation:

In a glass tube, 0.002 mmol of the preformed Rh-complexes, 36 mg (0.2 mmol) of the substrate and 4 ml of solvent, were mixed. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) that was purged 4 times with nitrogen and once with hydrogen. Then, the autoclave was pressurized with 10 bar of hydrogen. The reaction mixture was stirred for 8 h. The solvents were removed under vacuum. The residue was dissolved in 2 ml of MeOH and 0.3 ml of a 2M $TMSCHN_2$ solution in ether was added. A sample of the resulting mixture

was filtered over a silica plug and subjected to conversion and *e.e.* determination (capillary GC; CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12μm), 110°C; 3.4 (*R*), 3.9 (*S*)).

3.6 References

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[10] Cmc = critical micelle concentration. This is the minimum concentration at which micelles are being formed.

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Chapter 4
Monodentate Diamidophosphite Ligands

In this chapter the synthesis and application of monodentate diamidophosphites ligands in rhodium-catalyzed asymmetric hydrogenation are described.

4.1 Introduction

4.1.1 Diamidophosphites[1]

Phosphines are the most abundantly used chiral ligands in asymmetric hydrogenation.[2] To change the electronic properties of the phosphorus atoms of these ligands, electron donating or withdrawing groups can be introduced on the R moieties (Figure 4.1). Another method to tune these properties is to replace the carbon atom in the first coordination sphere[3] of the phosphorus by heteroatoms, like oxygen or nitrogen.

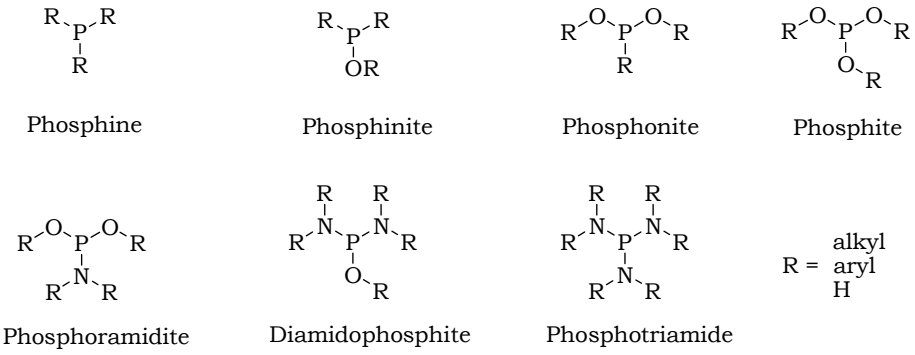


Figure 4.1: Phosphorus ligands.

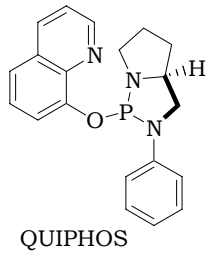
A number of successful ligands with heteroatoms in the first coordination sphere of phosphorus are the monodentate phosphonite,[4] phosphite[5] and phosphoramidite[6] ligands introdced by, respectively, the groups of Pringle, Reetz and Feringa, De Vries and Minnaard. These ligands led to excellent results in the rhodium-catalyzed asymmetric hydrogenation of a wide variety of prochiral substrates.[7] All of these ligands were based on BINOL (**2**).

Hardly any research has been done on the synthesis and application of chiral diamidophosphites. It is expected that these compounds have different properties compared to phosphoramidites or phosphites when applied as ligands in asymmetric catalysis. For example, introducing nitrogen substituents at the phosphorus creates more steric bulk around the phosphorus, compared to oxygen, due to the higher degree of substitution of nitrogen.[8] Furthermore, diamidophosphites are assumed to have a more electron-rich phosphorus compared to phosphoramidites or

phosphites. The combination of these factors could result in a catalyst with different activities or/and enantioselectivities.

4.1.2 Application of diamidophosphites

Only a few examples are known of diamidophosphites in asymmetric catalysis. Gavrilov and co-workers introduce in a series of articles different diamidophosphites, which all have an additional amine functionality as an extra coordination site.[9] These ligands gave modest to good *e.e.'s* in asymmetric allylic substitution reactions.



QUIPHOS

The most versatile diamidophospite has been developed by Buono and co-workers.[10] QUIPHOS has proved to be a versatile ligand for a variety of transition metal catalyzed asymmetric reactions, such as: palladium-catalyzed allylic substitutions,[11] copper-catalyzed Diels-Alder reactions[12] and copper-catalyzed conjugate addition reactions.[13]

An example of a diamidophosphite in an iridium-catalyzed allylic alkylation has been reported by Helmchen and co-workers. The obtained results were rather poor.[14] Reetz and co-workers have reported a series of diamidophosphites which have been tested in the rhodium-catalyzed asymmetric hydrogenation (see also §4.2.4, Figure 4.3).[15] The results were rather poor with a maximum of 30% *e.e.* in the hydrogenation of dimethyl itaconate (**39**).

Börner *et al.* and van Leeuwen *et al.* reported independently the use of diamidophosphites in the Rh-catalyzed hydroformylation of alkenes,[16] with modest results.

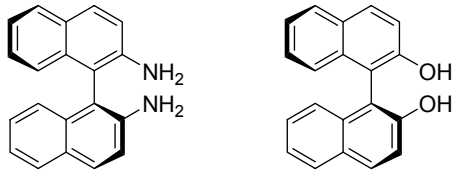
4.1.3 Goal of this research

The goal of this research is to synthesize a library of new monodentate diamidophosphites based on 1,1'-binaphthyl-2,2'-diamine. The option to introduce different substituents on the nitrogens makes it possible to create a library with a lot of structural variation. These new ligands will be tested in the rhodium-catalyzed asymmetric hydrogenation of prochiral alkenes.

4.2 Synthesis of 1,1'-binaphthyl-2,2'-diamine

4.2.1 Literature procedures

We anticipated to make a library of ligands based on 1,1'-binaphthyl-2,2'-diamine (**1**). Unfortunately, the price of the diamine is distinctly higher than the price of BINOL (2,2'-dihydroxy-1,1'-binaphthyl) (**2**).[17] Since the synthesis of **1** is well described, it was decided to synthesize it ourselves.



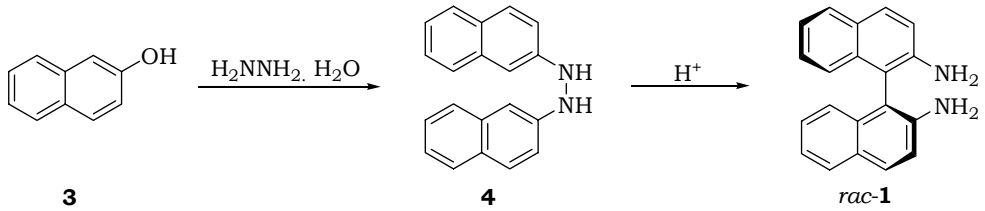
(*S*)-**1** (*S*)-**2**

Figure 4.2: 1,1'-Binaphthyl-2,2'-diamine (**1**) and BINOL (**2**).

4.2.1.1 Coupling of 2-naphthol

The shortest route to **1** is by a method reported by Clemo and Dawson[18]. 2-Naphthol (**3**) and hydrazine hydrate are heated in an autoclave to 170°C and stirred for 48 h (Scheme 4.1). The reaction is thought to proceed via a benzidine rearrangement,[19] with **4** as an intermediate, although the exact mechanism of this reaction is still under debate. The reaction can be performed on large scale with good yields. A disadvantage of this method is that the diamine is obtained as a racemic mixture which makes it necessary to perform a resolution afterwards, which has been described in literature.[20]

Unfortunately, several attempts to perform this synthesis failed. The reaction was performed on small scale in a Pyrex tube or on large scale in an autoclave. In all cases mixtures of 2-naphthol and the highly toxic 2-naphthylamine were obtained (see also § 4.2.1.2).[21] No further attempts were made to reproduce the reaction.[22]



3 **4** *rac*-**1**

Scheme 4.1: Synthesis of 1,1'-binaphthyl-2,2'-diamine (**1**) via benzidine rearrangement.[18]

4.2.1.2 Coupling of 2-naphthylamine

Another well known procedure is the homo-coupling of 2-naphthylamine.[23] As mentioned before, 2-naphthylamine is a highly toxic compound, which can cause cancer. The toxicology of 2-naphthylamine is described as follows in the material safety data sheets (MSDS):[24] *"A series of studies of workers with occupational exposure to it has shown clear evidence of a link between exposure and bladder cancer. In the UK it appears in Schedule 2 of the Control of Substances Hazardous to Health Regulations (COSHH) 1999 which prohibits its "manufacture and use for all purposes"."*[21] Due to the health risks it was decided to relinquish this strategy.

4.2.2 BINOL as starting material

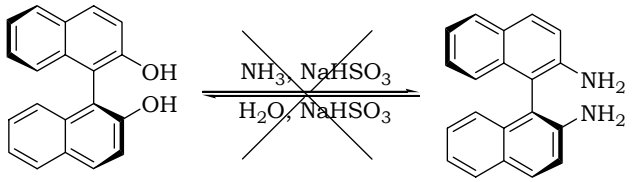
As mentioned before, BINOL (**2**) is a cheap starting material, of which both enantiomers can be obtained in pure form. With these features BINOL (**2**) would be an ideal starting material for the synthesis of **1**. But, to the best of our knowledge, there are no successful reactions known in which BINOL (**2**) is transformed into 1,1'-binaphthyl-2,2'-diamine (**1**).

4.2.2.1 Bucherer reaction

The most classical method to transform naphthols into the corresponding naphthyl amines is the Bucherer reaction,[25] in which a naphthol reacts with sodium bisulfite and ammonia to form the corresponding naphthyl amine. The reverse reaction is also known where a

naphthyl amine reacts with sodium bisulfite and water to form the corresponding naphthol.

Unfortunately, attempts to perform this reaction with BINOL (**2**) failed (Scheme 4.2). Only starting material was recovered. In the ^{1}H-NMR spectrum, traces of another aromatic system were observed, which probably is the sulphonated intermediate.



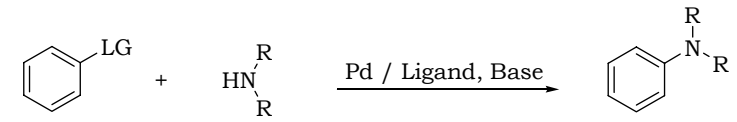
rac-**2** *rac*-**1**

Scheme 4.2: Attempted Bucherer reaction on BINOL (**2**).

4.2.2.2 Buchwald-Hartwig chemistry

A very elegant method to transfer BINOL (**2**) into 1,1'-binaphthyl-2,2'-diamine (**1**) would be a palladium-catalyzed coupling of an amine and a BINOL derivative. Buchwald and Hartwig developed a wide variety of Pd-catalysts to aminate aromatic systems.[26]

In a standard reaction an aryl compound with a good leaving group and an amine react under influence of a catalytic palladium source, a ligand and a base to form the corresponding arylated amine (Scheme 4.3).[27]



LG = Leaving Group

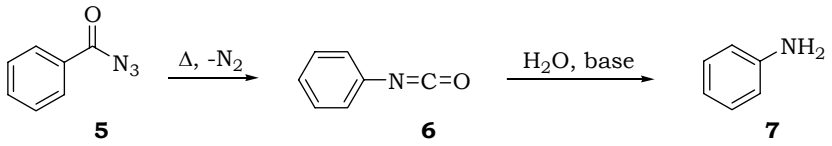
Scheme 4.3: Buchwald-Hartwig amination.

Frequently used leaving groups for these kinds of reactions are halides, and in particular bromides. Unfortunately, 2,2'-dibromo-1,1'-binaphthyl is not commercially available and should be synthesized. This can be achived from BINOL (**2**), but the disadvantage is that the temperature at which this

reaction is performed is 320°C. At these elevated temperatures BINOL (**2**) racemizes, which makes a resolution step necessary afterwards. Another frequently used leaving group is a triflate. The bistriflate of BINOL (**2**) can be synthesized in a straightforward reaction, with good yields. Unfortunately, attempts by Singer and Buchwald to substitute the bistriflate of BINOL (**2**) with an ammonia equivalent failed.[28]

4.2.2.3 Curtius Rearrangement

A classical method to introduce amine moieties on an aromatic system is the Curtius rearrangement (Scheme 4.4).[29]



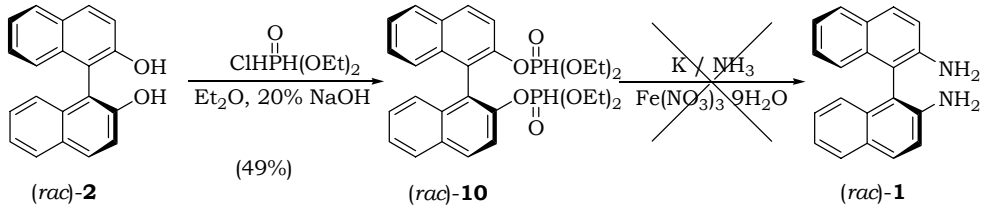
Scheme 4.4: Curtius Rearrangement.

Starting from the acyl azide **5**, the isocyanate **6** is formed with evolution of N_2 when the acyl azide **5** is heated. *Acyl azides can be explosive if isolated. To diminish the risks of explosions, acyl azides should preferably be kept in solution.*[30] Hydrolysis of the isocyanate **6** forms a unstable carbamic acid, which decomposes in the primary amine **7**. Reaction of the isocyanate with an alcohol or an amine would form respectively the corresponding carbamate or urea. The Curtius rearrangement of 1,1'-binaphthalenyl-2,2'-dicarboxylic acid (**16**) has been reported. Unfortunately, **16** is not commercially available and must be synthesized in a multistep synthesis.[31]

4.2.2.4 Other methods

Another method to transform hydroxy groups on an aromatic ring into an NH_2 group is by converting the hydroxy group first into an aryl diethyl phosphate. Treatment of this diethyl phosphate compound with potassium amide (K in liquid NH_3) and an iron catalyst ($Fe(NO_3)_3 \cdot 9H_2O$) yields the corresponding primary aromatic amines (Scheme 4.5).[32] The formation of the diphosphate **10** was straightforward and proceeded in moderate yield.

Unfortunately, the second reaction, the transformation of **10** into **1** did not proceed and only starting material was recovered.



(*rac*)-**2** (*rac*)-**10** (*rac*)-**1**

Scheme 4.5: Attempted synthesis of 1,1'-binaphthyl-2,2'-diamine.

4.2.3 Multistep synthesis of (±)-1

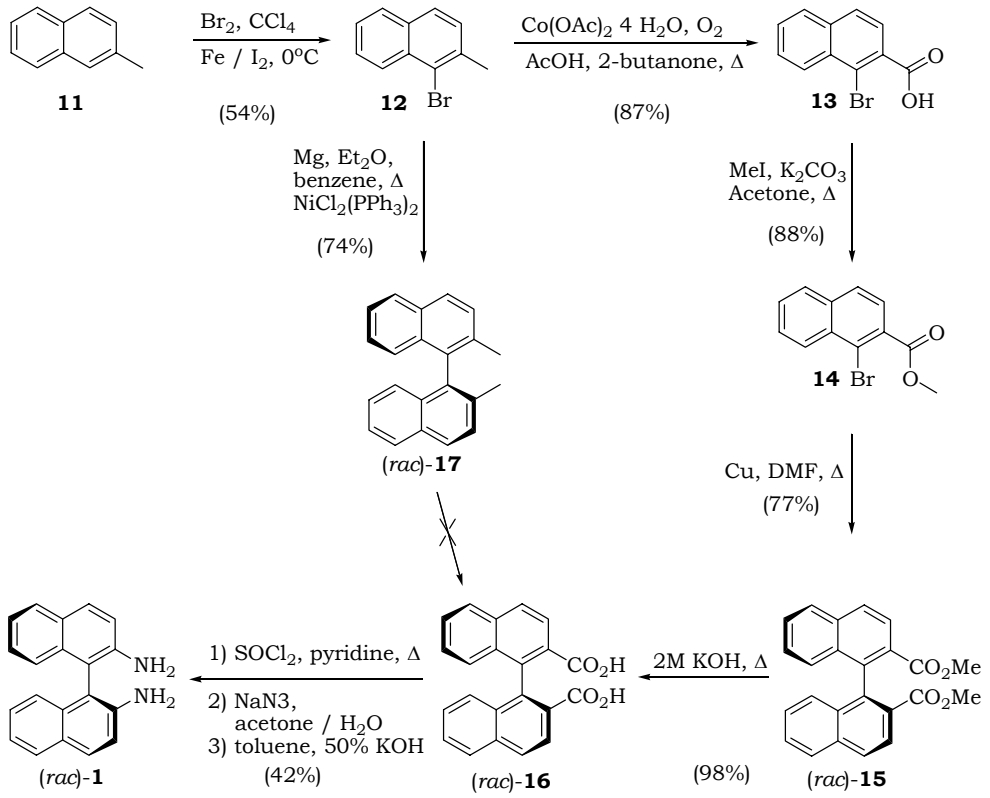
Since all previous mentioned methods failed or were not suitable, a multistep synthesis was designed based on a Curtius rearrangement. The synthesis is depicted in Scheme 4.6.

In the first step, commercially available 2-methylnaphthalene (**11**) was brominated, according to a procedure described by Adams and Binder.[33] The reaction proceeded by slow addition of the bromine (>7 h for 1 mol) under exclusion of light. A modest yield was obtained, probably due to side-reactions, such as overbromination.

The 1-bromo-2-methylnaphthalene (**12**) was oxidized to the corresponding carboxylic acid, by a $Co(OAc)_2 \cdot 4H_2O$ mediated oxidation reaction with molecular oxygen, as described by Bringmann *et al.*[34] The product was obtained in a good yield. Refluxing **12** in acetone with K_2CO_3 and MeI resulted in formation of 1-bromo-2-naphthoic acid methyl ester (**13**).

Coupling of **13**, under the standard Ullmann coupling conditions, according to a method described by Seki *et al.*,[35] gave the corresponding binaphthalene in good yield. Besides the desired product, 14% of the dehalogenated substrate was isolated, which is a common side-product of the Ullmann coupling (not shown).[36] Direct coupling of **13** to form **16** is not possible under standard Ullmann conditions. Attempts to perform the coupling reaction under the milder conditions developed by Lin *et al.*[37] were unsuccessful.

Diacid **16** was obtained almost quantitatively after saponification of **15** in refluxing 2M KOH. Refluxing of **16** in $SOCl_2$ with pyridine gave the corresponding diacid dichloride (not shown). A subsequent nucleophilic substitution with NaN_3 gave the dicarboxylic azide (not shown), which was subjected to a Curtius rearrangement under aqueous conditions to give 1,1'-bisnaphthyl-2,2'-diamine **1** in 42% yield over three steps.[31]



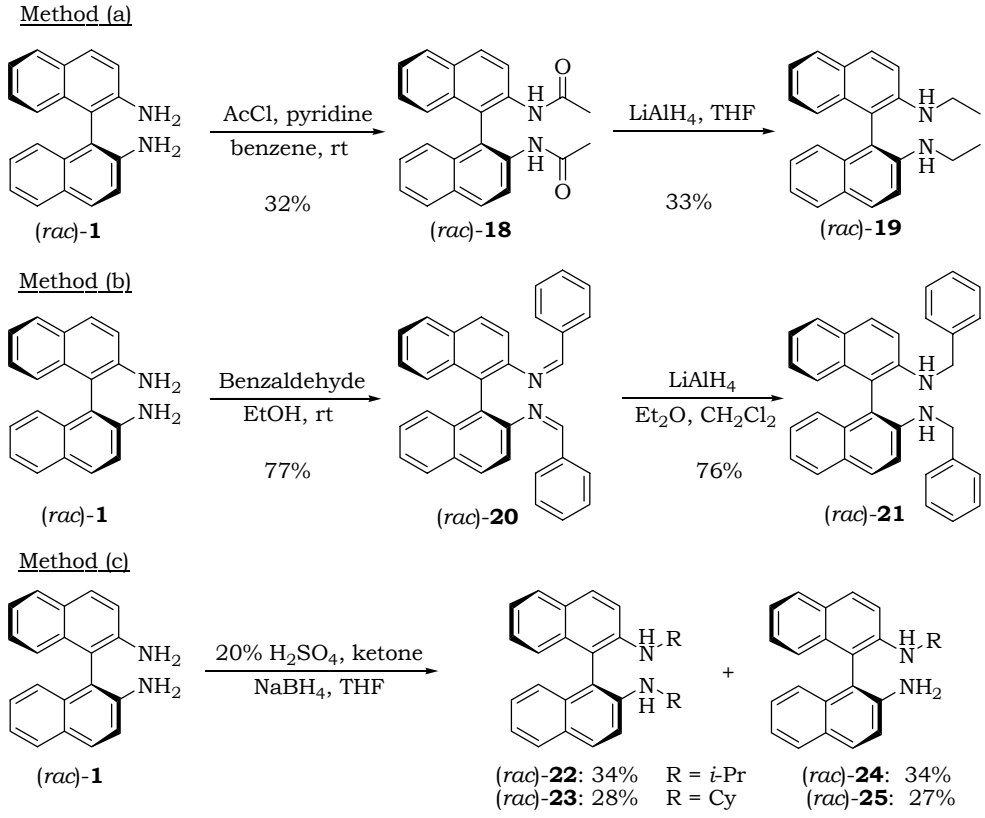
Scheme 4.6: Synthesis of 1,1'-bisnaphthyl-2,2'-diamine (**1**).

A shorter route to **1** would be the direct coupling of **12**, followed by oxidation of **17**. A Curtius rearrangement of **16** would then give the desired 1,1'-bisnaphthyl-2,2'-diamine (**1**) in only four steps from 2-methyl-naphthalene (**11**). The coupling of **12** went smooth via the $NiCl_2(PPh_3)_2$ catalyzed homo-coupling of **12** with its corresponding Grignard reagent. Unfortunately, attempts to oxidize **17** failed. No conversion was observed when the previously described $Co(OAc)_2 \cdot 4H_2O$ method was used. Even

under more harsh conditions, using $KMnO_4$ as an oxidant, no product could be isolated.

4.2.4 Attempts to make 1,1'-bisnaphthyl-2,2'-diamine (1)-based diamidophosphites

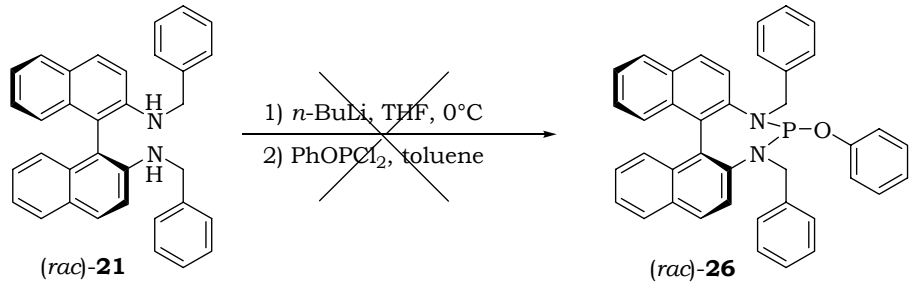
Racemic 1,1'-bisnaphthyl-2,2'-diamine (**1**) was used to study the synthesis and stability of 1,1'-bisnaphthyl-2,2'-diamine (**1**) based diamidophosphites. Racemic **1** was alkylated at the amine moieties using two different approaches. Compounds **19** and **21** were synthesized in a two step procedure via the corresponding acyl amide or aldimine / ketimine. Subsequent reduction of these compounds gave the *N,N*'-alkylated compounds (Scheme 4.7a and Scheme 4.7b).



Scheme 4.7: Synthesis of *N*,N-alkylated 1,1'-binaphthyl-2,2'-diamines.

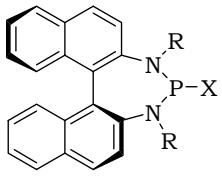
Kočovskỳ and co-workers reported a one-pot reaction for the alkylation of **1,** in which different alkyl groups were introduced in good yields.[38] Several attempts to repeat these reactions, never led to the same yields. In addition to the desired dialkylated products, large amounts of monoalkylated products were obtained. The mixture of mono- and dialkylated products could be separated by column chromatography (see §4.5). Furthermore, the total yield was rather disappointing (Scheme 4.7c).

Unfortunately, attempts to synthesize diamidophosphites from the *N,N'* -dialkylated products failed. In all cases hydrolyzed or oxidized products were obtained. For example, the attempted synthesis of **26** is shown in Scheme 4.8. Bulky amines react in general slowly with phosphoro(di)chloridites. To make them more reactive, the Li-amide was formed with *n*-BuLi. The amide reacts then with the corresponding phosphorochloridite to form the ligand.



Scheme 4.8: Attempted synthesis of diamidophosphites.

During our research an article by Reetz and co-workers was published,[15] in which the synthesis and application of diamidophosphites were reported. They isolate the ligands as their corresponding BF_3-adducts. Attempts to deprotect the ligands and to purify them failed. The ligands were deprotected in situ and used as obtained. Only ligand a in Figure 4.3 led to a reasonable conversion (80%) and a modest *e.e.* (30%) in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate (**39**) (1.3 bar H_2; CH_2Cl_2; 20 h).[15] All other tested ligands gave conversions of only 2-10%. Based on our own experience and the results reported by Reetz et al. it was decided not to continue the attempts.



a) R = CH_3; X = OCH_3
b) R = CH_3; X = NEt_2
c) R = Ph; X = OCH_3
d) R = Ph; X = CH_3
e) R = Ph; X = $CH(CH_3)_2$
f) R = Ph; X = c-C_6H_{11}
g) R = Ph; X = $C(CH_3)_3$

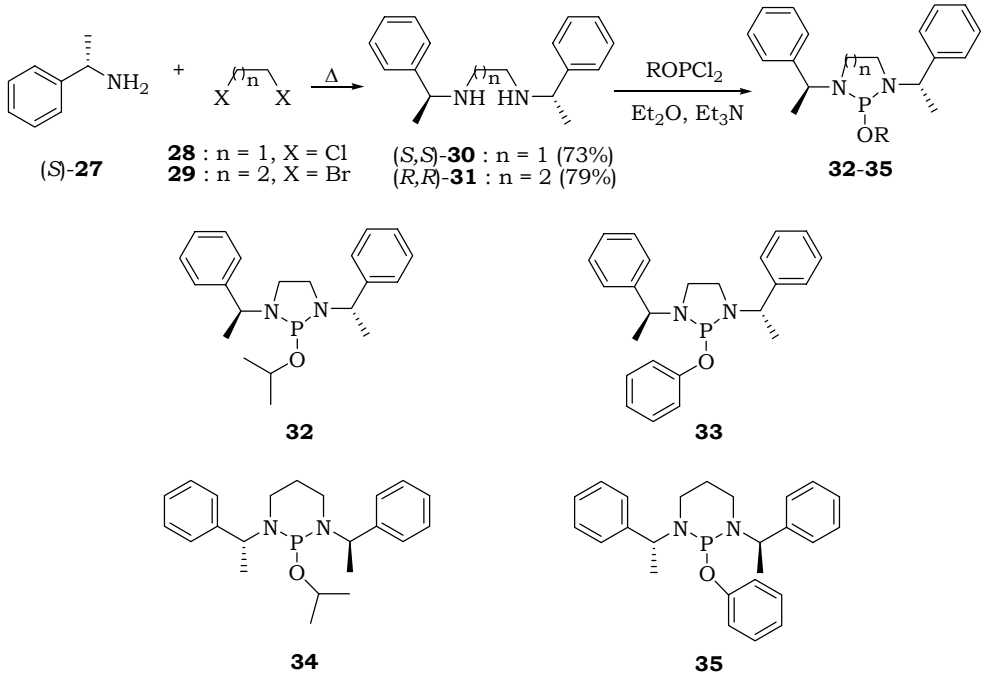
Figure 4.3: Diazaphospholidines synthesized by Reetz and co-workers.[15]

4.3 Diamidophosphites based on α-phenylethylamine

4.3.1 Synthesis of ligands

To study the properties of monodentate diamidophosphite ligands, simplified model compounds were synthesized. These compounds were based on diamines **30** and **31**. The synthesis of these diamines is straightforward, with the cheap α-phenylethylamine (**27**) and the corresponding dihaloalkanes **28** and **29** as starting materials (Scheme 4.9).

The reaction of amines **30** and **31** with dichlorophosphites gave the desired diamidophosphites **32**-**35**. The crude products were used as obtained. All ligands were pure according to ^{31}P-NMR. The values of the ^{31}P signals are in the range of 122-125 ppm. This is in the same range of those of phosphites and about 20 ppm smaller than phosphoramidites.[39] On the other hand, traces of free (up to 5%) amine were observed in the ^{1}H- and ^{13}C-NMR spectra. Any attempt to purify the products failed. The compounds are unstable on silica as well as on Al_2O_3.[40] Purification by distillation has not been attempted, since distillation under reduced pressure of structural similar compounds resulted in violent explosions.[41]



Scheme 4.9: Synthesis of ligands **32-35**.

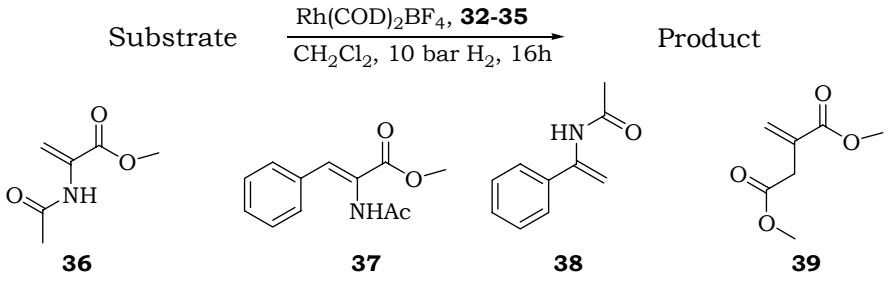
4.3.2 Hydrogenation experiments

Ligands **32-35** were tested in the rhodium-catalyzed asymmetric hydrogenation of four benchmark substrates. The results are depicted in Table 4.1.

All reactions were run for 16 h with a H_2-pressure of 10 bar and 1 mol% of catalyst. In general the ligands performed disappointingly. No full conversion has been obtained and the enantioselectivities were low to modest. The best results were obtained for substrate **38** with ligands **32** and **33**; 31% and 12% *e.e.*, at 30% and 46% conversion, respectively. Surprisingly, despite the fact that both ligands have the same configuration, opposite configurations of the products were obtained. Although no hard conclusion can be drawn from the results, a small trend can be observed. Introduction of a phenol group in the ligands increases the reaction rate. Higher conversions have been observed for ligands **33** and **35** compared to their 2-propanol analogues **32** and **34**. Remarkably,

is also the fact that the best results (t.o.n. and *e.e.'s*) were obtained with substrate **38**. As already mentioned in chapter 2, turnover numbers of the hydrogenation of enamides are in general lower than those for α-dehydroamino acids.

Table 4.1: The rhodium-catalyzed hydrogenation of benchmark substrates **36**-**39** with diamidophosphite ligands **32**-**35**.[a,b]



36 **37** **38** **39**

Entry	*Ligand*	*Substrate*[c,d]			
		36	**37**	**38**	**39**
1	**32**	10 (17)	0 (5)	31 (30)	9 (2)
2	**33**	0 (72)	0 (19)	12 (46)	5 (6)
3	**34**	0 (6)	0 (6)	0 (10)	0 (5)
4	**35**	6 (20)	0 (2)	0 (13)	5 (5)

(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of solvent with 0.002 mmol of $Rh(COD)_2BF_4$ and 0.004 mmol of diamidophosphite (b) Reactions were run for 16 h (c) *E.e.'s* were determined by chiral GC (for details see experimental section), conversion are indicated in brackets (d) In all cases the *R* enantiomer of ligand gave the *S* enantiomer of products.

The poor results obtained for ligands **32**-**35** are most likely caused by the sensitivity of these ligands. Since purification was troublesome, crude ligands have been used. These ligands might have contained traces of free amines which can interfere with the hydrogenation.

4.4 Conclusion

A successful synthesis of 1,1'-binaphthyl-2,2'-diamine (**1**) is described, in which the desired product can be obtained in 6 steps. The reactions could be performed on multigram scale with reasonable to excellent yields. Unfortunately, attempts to make diamidophosphites ligands based on **1** failed.

The synthesis of diamidophosphites based on α-phenylethylamine (**27**) was successful. Purification of these ligands was not possible and the crude ligands were used as obtained. The ligands were tested in rhodium-catalyzed asymmetric hydrogenation of four benchmark substrates. The results were disappointing. Low conversions, and only in a few cases optically active products were obtained.

The high instability towards hydrolysis makes it difficult to isolate and purify diamidophosphites. The high instability is probably caused by the basic character of the nitrogens. It is known that the nitrogen of a P-N bond in a phosphoramidite has a strong sp^2-character.[42] Presumably, in a diamidophospite, one of the nitrogens has a strong sp^2-character, while the other has a strong sp^3-character. The sp^3-hybridized nitrogen will be more basic then the sp^2-hybridized one. A possibility to stabilize these ligands might be the introduction of electron-withdrawing groups on the nitrogens, since these groups stabilize the nitrogen phosphorus bond.[16a,b] The disappointing results obtained so far in hydrogenation reactions might be caused by the impurities in the ligands. The stability, easy synthesis and excellent results obtained, makes phosphoramidites and phosphites a more versatile and interesting class of ligands compared to the corresponding diamidophosphites.

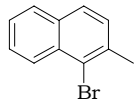
4.5 Experimental section

General remarks:

For general remarks see Chapter 2.

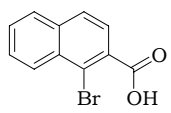
General procedure hydrogenations:

In a glass tube, 0.81 mg (2 µmol) of $Rh(COD)_2BF_4$, 4 µmol of ligand (2 eq.), 200 µmol of the substrate and 4 ml of solvent, were added. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) that was purged 4 times with nitrogen and once with hydrogen. Then, the autoclave was pressurized with 10 bar of hydrogen. The reaction mixture was stirred for 16 h. A sample of the resulting mixture was filtered over a silica plug and subjected to conversion (^{1}H-NMR) and *e.e.* determination (capillary GC). Absolute configurations were determined by comparison with reference compounds (**36**, **38** and **39**) or compared to literature values (GC injection; **37**).[43]

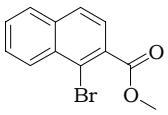


1-Bromo-2-methyl-naphthalene (**12**).[33] To a cooled (0°C) solution of 142 g (1.00 mol) 2-methylnaphthalene (**11**) in 300 ml of CCl_4 was added a catalytic amount of Fe powder and I_2. The solution was shielded from light. To this solution was added 162 g (1.01 mol) Br_2 in 300 ml of CCl_4 over a period of 7 h. The temperature was not allowed to rise above 5°C. The mixture was stirred overnight at rt after the last addition. The reaction mixture was washed with 10% $NaOH_{(aq)}$ (5x 200 ml), water (2x 200 ml) and brine (200 ml). The organic layer was separated and dried over $CaCl_2$, filtered and concentrated in vacuum. The crude mixture was purified by vacuum distillation. The product was obtained as yellow oil at 126-128°C (4 mbar). Yield: 119.3 g (0.54 mol; 54%) **^{1}H-NMR** (300 MHz, $CDCl_3$):[44] δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 2.59 (s, 3H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 136.0 (s), 133.0 (s), 132.5 (s), 128.7 (d), 128.0 (d), 127.0 (d), 126.9 (d), 125.6 (d), 124.0 (s), 24,2 (q); **HRMS** for $C_{11}H_9Br$: calcd. 219.989 found 219.989.

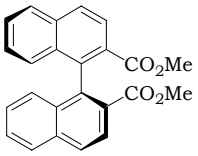
1-Bromo-naphthalene-2-carboxylic acid (**13**).[34] A mixture of 26.3 g (0.12 mol) **12**, 5.90 g (24.0 mmol) $Co(OAc)_2{\cdot}4H_2O$, 3.20 ml (36 mmol) 2-butanone in 100 ml acetic acid was heated in an autoclave to 120°C. The mixture was stirred overnight under a constant pressure of 4 bar O_2. The autoclave was cooled to room temperature and the pressure was released. The mixture was poured into 400 ml ice-water and the precipitate was collected, washed with water



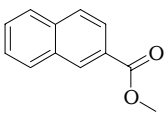
and dried in a vacuum oven at 60°C. The product was obtained as a slightly brown solid. Yield: 26.3 g (0.10 mol; 87%) **^{1}H-NMR** (300 MHz, DMSO-d_6):[45] δ 13.59 (bs, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.02-7.98 (m, 2H), 7.73-7.62 (m, 3H); **^{13}C-NMR** (75.48 MHz, DMSO-d_6):[45] δ 168.0 (s), 133.9 (s), 133.0 (s), 130.8 (s), 128.1 (d), 128.0 (d), 127.7 (d), 127.5 (d), 126.9 (d), 124.9 (d), 119.4 (s); **HRMS** for $C_{11}H_7BrO_2$: calcd. 249.963 found 249.964.



1-Bromo-naphthalene-2-carboxylic acid methyl ester (**14**).[35] A suspension of 6.35 g (25.3 mmol) **13**, 10.9 g (79.0 mmol) K_2CO_3 and 8.00 ml (128 mmol) MeI in 70 ml acetone was refluxed for 6 h. The mixture was filtered and the filtrate was concentrated in vacuo. The product was purified by column chromatography (SiO_2; hexane/EtOAc 6:1; R_f = 0.50). The product was obtained as a yellow solid. Yield 5.88 g (22.2 mmol; 88%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[46] δ 8.36 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.61-7.46 (m, 3H), 3.94 (s, 3H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 167.7 (s), 135.0 (s), 132.0 (s), 131.0 (s), 128.4 (d), 128.0 (d), 128.0 (d) (2x), 127.7 (d), 125.6 (d), 122.5 (s), 52.6 (q); **HRMS** for $C_{12}H_9BrO_2$: calcd. 263.979 found 263.979.

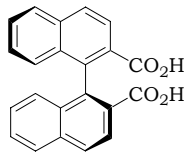


(±)-[1,1']Binaphthalenyl-2,2'-dicarboxylic acid dimethyl ester (**15**).[35] A mixture of 26.7 g (0.10 mol) **14** and 40.0 g activated Cu-powder in 250 ml freshly distilled DMF was refluxed overnight (16 h) under an argon atmosphere. The mixture was filtered and the residue was boiled in toluene. The organic layers were combined, washed with 2M $HCl_{(aq)}$, water and dried on Na_2SO_4. After removal of Na_2SO_4 by filtration, the organic layer was concentrated. The product was purified by column chromatography (SiO_2; hexane/EtOAC 10:1; R_f = 0.21). The product was obtained as a white solid. Yield: 14.4 g (38.9 mmol; 77%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[46] δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.47 (dd, *J* = 7.7 Hz, 7.3 Hz, 2H), 7.19 (dd, *J* = 8.1 Hz, 7.3 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.46 (s, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 167.0 (s), 140.3 (s), 134.8 (s), 132.8 (s), 127.9 (d), 127.8 (d), 127.6 (d), 127.2 (d), 127.0 (s), 126.6 (d), 125.8 (d), 51.8 (q); **HRMS** for $C_{24}H_{18}O_4$: calcd. 370.120 found 370.120.

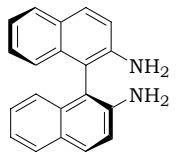


As a side product, naphthalene-2-carboxylic acid methyl ester was isolated as a white solid. (SiO_2; hexane/EtOAc 10:1; R_f = 0.50). Yield: 2.79 g (15 mmol; 15%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.07 (dd, *J* = 8.8 Hz, 1.46 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.62-7.51 (m, 2H), 3.99 (s, 3H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 167.2 (s), 135.4 (s), 132.4 (s), 131.0 (d), 129.3 (d), 128.2 (d), 128.1 (d), 127.7 (d), 127.3 (s),

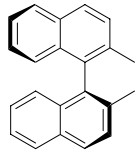
126.6 (d), 125.2 (d), 52.2 (q); **HRMS** for $C_{12}H_{10}O_2$: calcd. 186.068 found 186.067.



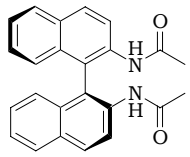
(±)-[1,1']Binaphthalenyl-2,2'-dicarboxylic acid (**16**). A suspension of 14.4 g (38.9 mmol) **15** in 500 ml 2M $KOH_{(aq)}$ was heated at reflux overnight. The mixture was cooled and extracted with CH_2Cl_2 (200 ml). The aqueous layer was acidified with conc. $HCl_{(aq)}$ and the white precipitate was collected and dried in the air. The product was obtained as a white solid. Yield: 13.0 g (38.0 mmol; 98%). **^{1}H-NMR** (300 MHz, DMSO-d_6):[47] δ 12.42 (bs, 2H), 8.10 (s, 4H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 7.7 Hz, 7.3 Hz, 2H), 7.27 (dd, *J* = 8.1 Hz, 7.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H); **^{13}C-NMR** (75.48 MHz, DMSO-d_6):[47] δ 167.2 (s), 139.0 (s), 133.8 (s), 132.0 (s), 127.6 (s), 127.5 (d), 127.1 (d), 127.0 (d), 126.2 (d) (2x), 125.6 (d); **HRMS** for $C_{22}H_{14}O_4$: calcd. 342.089 found 342.090.



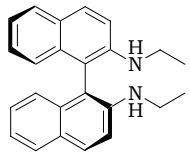
(±)-[1,1']Binaphthalenyl-2,2'-diamine (**1**).[31] 13.0 g (38.0 mmol) **16**, was refluxed in 120 ml $SOCl_2$ and 4.60 ml pyridine. The solution was concentrated and the remaining oil was dissolved in 100 ml CCl_4. The precipitate was removed by filtration and the filtrate was concentrated to yield a yellow solid. The solid was dissolved in 80 ml acetone. 13.2 g (0.20 mol) NaN_3 in 35 ml water was added dropwise to this solution. The solution was cooled in an ice-bath and 120 ml water was added. The mixture was stored in the refrigerator over the weekend. The precipitate was collected after warming to room temperature. The solid was dissolved in 200 ml toluene and the solution dried over $CaCl_2$. The solution was filtered and the organic solution was heated at 50°C for 30 min and then 90 min at reflux. 50 ml of a 50% $KOH_{(aq)}$ solution was added to the hot stirred solution. The mixture was refluxed for an additional 90 min. The toluene layer was separated, 200 ml 6M $HCl_{(aq)}$ was added and the resulting mixture heated for 15 min. The acidic aqueous layer was separated, filtered and neutralized with concentrated NaOH. The precipitate was collected and dried in air. The product was obtained as off white solid after recrystallization from EtOH/acetone. Yield 4.53 g (16 mmol; 42%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[50] δ 7.78-7.75 (m, 4H), 7.23-7.02 (m, 8H), 3.60 (bs, 4H); **^{13}C-NMR** (75.48 MHz, DMSO-d_6): δ 142.6 (s), 133.6 (s), 129.4 (d), 128.4 (s), 128.1 (d), 126.8 (d), 123.9 (d), 122.4 (d), 118.3 (d), 112.5 (s); **HRMS** for $C_{20}H_{16}N_2$: calcd. 284.131 found 284.132.



(±)-2,2'-Dimethyl-[1,1']binaphthalenyl (**17**).[48] To 2.00 g (83.3 mmol) Mg in 10 ml ether was added dropwise a solution of 16.3 g (13.8 mmol) **12** in 60 ml ether/benzene (1:1). The mixture was stirred at reflux for 1 h after the addition was completed. To the solution of Grignard reagent was added 0.50 g (0.76 mmol) $NiCl_2(PPh_3)_2$. To this mixture was added dropwise a solution of 14.8 g (67.0 mmol) **16** in 30 ml ether. The reaction mixture was refluxed overnight. The reaction was quenched with 2M $HCl_{(aq)}$. The layers were separated and the aqueous layer was extracted twice with ether. The organic layers were washed with water, brine and dried on Na_2SO_4. The solution was concentrated after removal of the Na_2SO_4. The crude product was purified by bulb-to-bulb distillation. The product was obtained as a yellow sticky gum. (250-300°C / 0.5 mbar). Yield: 14.0 g (49.6 mmol; 74%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[49] δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 8.1 Hz, 7.0 Hz, 2H), 7.18 (dd, *J* = 8.1 Hz, 7.0 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 2.02 (s, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 135.1 (s), 134.3 (s), 132.7 (s), 132.2 (s), 128.7 (d), 127.9 (d), 127.4 (d), 126.1 (d), 125.6 (d), 124.9 (d), 20.0 (q); **HRMS** for $C_{22}H_{18}$: calcd. 282.141 found 282.141.



(±)-*N*-(2'-Acetylamino-[1,1']binaphthalenyl-2-yl)-acetamide (**18**).[50] 1.20 g (4.23 mmol) **1** and 1.00 ml (14.0 mmol) acetyl chloride were dissolved in 8 ml pyridine and 40 ml benzene. The mixture was stirred overnight at room temperature. The reaction was quenched with 10% $NaOH_{(aq)}$ (100 ml). The solid was removed by filtration. The aqueous solution was extracted with benzene (2x 50 ml). The combined organic layers were washed with brine, dried on $MgSO_4$, filtered and concentrated. The remaining solid was crystallized from EtOH/hexane. The product was obtained as an off-white powder. Yield 0.50 g (1.36 mmol; 32%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[50] δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.46 (dd, *J* = 8.1 Hz, 7.0 Hz, 2H), 7.33 (dd, *J* = 8.4 Hz, 6.6 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.95 (bs, 2H), 1.84 (s, 6H);

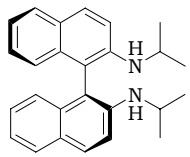


(±)-N^2,$N^{2'}$-Diethyl-[1,1']binaphthalenyl-2,2'-diamine (**19**).[50] A suspension of 0.50 g (1.35 mmol) **18** and 0.30 g $LiAlH_4$ in 35 ml freshly distilled THF was refluxed for 3 h. The reaction mixture was cooled to room temperature and quenched with 5 ml water and 5 ml 15% $NaOH_{(aq)}$. The white precipitate was removed by filtration and the residue was washed thoroughly with ether. The combined organic layers were washed with water, brine, dried on Na_2SO_4, filtered and concentrated. The crude product was purified with column chromatography (SiO_2; hexane/EtOAc 9:1; R_f = 0.53). The product was obtained as a white solid.

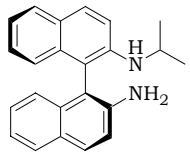
Yield: 150 mg (0.44 mmol; 33%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[50] δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.10-7.23 (m, 6H), 6.95 (d, *J* = 7.7 Hz, 2H), 3.59 (bs, 2H), 3.20 (q, *J* = 7.1 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 144.6 (s), 133.9 (s), 129.5 (d), 128.0 (d), 127.6 (s), 126.6 (d), 123.8 (d), 121.8 (d), 114.2 (d), 112.1 (s), 38.6 (t), 12.2 (q); **HRMS** for $C_{24}H_{24}N_2$: calcd. 340.194 found 340.193.

General procedure for the synthesis of **22** and **23**:[38]

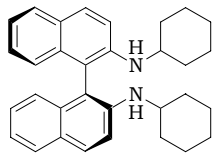
To a solution of 14 mmol of the corresponding ketone in 10 ml THF and 20% $H_2SO_{4(aq)}$ was added over a period of 10 min, simultaneously, a solution of 284 mg (1 mmol) **1** in 10 ml THF and 530 mg (14 mmol) solid $NaBH_4$. The mixture was stirred for an additional 15 min at room temperature. The mixture was poured into 100 ml 2% $KOH_{(aq)}$ and extracted with EtOAc (3x 20 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The remaining crude mixtures were purified by column chromatography (SiO_2; toluene). The products were obtained as white solids.



(±)-*N*,*N*'-Diisopropyl-[1,1']binaphthalenyl-2,2'-diamine (**22**). R_f = 0.51. Yield 125 mg (0.34 mmol; 34%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[38] δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.21-7.08 (m, 4H), 6.90 (d, *J* = 8.1 Hz, 2H), 3.77 (m, 2H), 3.38 (bs, 2H), 1.04 (d, *J* = 6.2 Hz, 6H), 0.95 (d, *J* = 6.2 Hz, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[38] δ 143.1 (s), 134.0 (s) (2x), 129.5 (d), 127.9 (d), 127.6 (s), 126.5 (d), 124.0 (d), 121.8 (d), 115.0 (d), 44.6 (d), 23.2 (q); **HRMS** for $C_{26}H_{28}N_2$: calcd. 368.225 found 368.224.

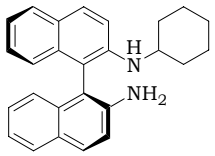


(±)-*N*'-Isopropyl-[1,1']binaphthalenyl-2,2'-diamine (**24**). R_f = 0.29. Yield 112 mg (0.34 mmol; 34%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[38] δ 7.88-7.76 (m, 4H), 7.29-6.96 (m, 8H), 3.78 (q, *J* = 6.2 Hz, 1H), 3.49 (bs, 3H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[38] δ 143.9 (s), 142.5 (s), 133.9 (s), 133.6 (s), 129.4 (d) (2x), 128.3 (s), 128.0 (d) (2x), 127.2 (s), 126.6 (d) (2x), 124.0 (d),123.8 (d), 122.3 (d), 121.9 (d), 118.2 (d), 115.2 (d), 113.0 (s), 112.1 (s), 44.7 (d), 23.2 (q), 23.1 (q); **HRMS** for $C_{23}H_{22}N_2$: calcd. 326.178 found 326.179.

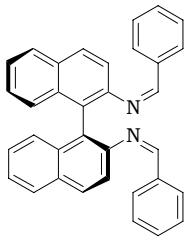


(±)-*N*,*N*'-Dicyclohexyl-[1,1']binaphthalenyl-2,2'-diamine (**23**). R_f = 0.71. Yield 125 mg (0.28 mmol; 28%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[38] δ 7.81 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 9.2 Hz, 2H), 7.15-7.06 (m, 4H), 6.88 (d, *J* = 7.7 Hz, 2H), 3.48 (bs, 2H),

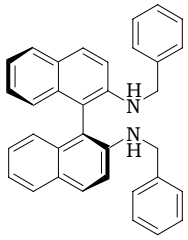
3.38-3.32 (m, 2H), 2.13-1.78 (m, 4H), 1.60-1.49 (m, 6H), 1.31-1.14 (m, 4H), 1.04-0.92 (m, 4H), 0.88-0.71 (m, 2H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[38] δ 143.9 (s), 134.0 (s), 129.3 (d), 127.5 (s), 127.9 (d), 126.4 (d),124.0 (d), 121.7 (d), 115.0 (d), 112.2 (s), 52.0 (d), 33.6 (t), 25.7 (t), 25.0 (t); **HRMS** for $C_{32}H_{36}N_2$: calcd. 448.288 found 448.289.



(±)-*N*'-Cyclohexyl-[1,1']binaphthalenyl-2,2'-diamine (**25**). R_f = 0.28. Yield 98 mg (0.27 mmol; 27%). **^{1}H-NMR** (300 MHz, $CDCl_3$):[38] δ 7.82 (d, *J* = 9.2 Hz, 1H), 7.78-7.73 (m, 3H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.21-7.08 (m, 5H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 3.60 (bs, 3H), 3.38-3.29 (m, 1H), 1.92-1.78 (m, 2H), 1.59-1.48 (m, 3H), 1.30-1.12 (m, 2H), 1.05-0.72 (m, 3H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[38] δ 143.8 (s), 142.9 (s), 133.9 (s), 133.8 (s), 129.4 (d), 129.4 (d) (2x), 128.4 (s), 128.0 (d) (2x), 128.0 (d) (2x), 127.5 (s), 126.6 (d), 126.6 (d), 124.1 (d), 123.7 (d), 122.3 (d), 121.8 (d), 118.2 (d), 115.2 (d), 112.6 (s), 112.3 (s), 52.1 (d), 33.8 (t), 33.6 (t), 25.6 (t), 25.0 (t), 24.9 (t); **HRMS** for $C_{26}H_{26}N_2$: calcd. 366.210 found 366.208.

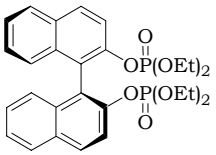


(±)-*N*,*N*'-Bis-[1-phenyl-meth-(Z)-ylidene]-[1,1']binaphthalenyl-2,2'-diamine (**20**). Diamine **1** (1.01 g (3.56 mmol) was dissolved in 20 ml EtOH. 0.90 ml (8.92 mmol) benzaldehyde was added and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated and the remaining solid was washed with pentane. The product was obtained as a white solid. Yield: 1.26 g (2.74 mmol; 77%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 8.15 (s, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.41-6.99 (m, 18H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 160.6 (d), 148.9 (s), 136.3 (s), 133.5 (s), 131.5 (s), 130.8 (d), 129.0 (d), 128.4 (d), 128.3 (d), 127.9 (d), 126.7 (d), 126.3 (d), 126.1 (s), 124.6 (d), 119.2 (d); **HRMS** for $C_{34}H_{24}N_2$: calcd. 460.193 found 460.193.

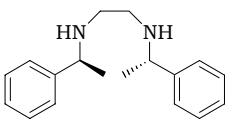


(±)-*N*,*N*'-Dibenzyl-[1,1']binaphthalenyl-2,2'-diamine (**21**). To a suspension of 57.0 mg (1.50 mmol) $LiAlH_4$ in 5 ml Et_2O was added dropwise a solution of 301 mg (0.65 mmol) **20** in 10 ml Et_2O/CH_2Cl_2 (1:1). The mixture was stirred overnight at room temperature. The reaction was quenched with concentrated HCl until a clear solution was obtained. The aqueous layer was separated. Concentrated NaOH was added and the layer was extracted with CH_2Cl_2. Organic layers were washed with brine, dried on Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2; toluene (drop of Et_3N)). The product was obtained as a white solid. Yield: 228 mg (0.49 mmol; 76%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.80-7.73

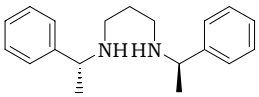
(m, 4H), 7.20-7.03 (m, 18H), 4.38 (s, 4H), 4.20 (bs, 2H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 144.2 (s), 139.8 (s), 133.8 (s), 129.6 (d), 128.4 (d), 128.1 (d), 127.7 (s), 126.9 (d), 126.7 (d), 126.7 (d), 123.9 (d), 122.0 (d), 114.1 (d), 112.0 (s), 47.5 (t); **HRMS** for $C_{34}H_{28}N_2$: calcd. 464.225 found 464.225.



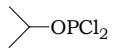
(±)-[2'-(Diethoxy-phosphoryl)-[1,1']binaphthalenyl-2-yl]-phosphonic acid diethyl ester (**10**).[51] (+/-)-Bis-*β*-naphthol (**2**) (10.0 g (35.0 mmol) was dissolved in 300 ml ether and the solution was cooled to 0°C. To this solution was added simultaneously dropwise 11.0 ml (76.0 mmol) diethyl chlorophosphate and 10 ml 20% $NaOH_{(aq)}$. The resulting mixture was stirred for 1 h at 0°C and then slowly warmed to room temperature where upon the mixture was stirred for an additional 3 h. The organic layer was washed with 10% $NaOH_{(aq)}$ (2x 50 ml), water (50 ml), brine (50 ml) and dried on Na_2SO_4. The mixture was filtered and concentrated in vacuo. The remaining yellow solid was recrystallized from EtOAc/hexane. The product was obtained as a white solid. Yield: 9.6 g (17.2 mmol: 49%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.35-7.30 (m, 1H), 7.21-7.19 (m, 2H), 3.69-3.56 (m, 2H), 3.45-3.35 (m, 2H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.74 (t, 7.0 Hz, 3H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$): δ -7.96; **^{13}C-NMR** (101.0 MHz, $CDCl_3$): δ 146.5(s, J_{P-C} = 6.11 Hz), 133.3 (s), 130.6 (s), 129.8 (d), 127.7 (d), 126.7 (d), 125.9 (d), 125.2 (d), 121.3 (s, J_{P-C} = 8.43 Hz), 119.0 (d), 64.1 (t, J_{P-C} = 18.3 Hz), 64.0 (t, J_{P-C} = 19.5 Hz), 15.5 (q, J_{P-C} = 15.9 Hz), 15.4 (q, J_{P-C} = 14.7 Hz); **HRMS** for $C_{28}H_{32}O_8P$: calcd. 558.157 found 558.156.



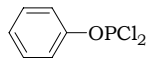
(*S,S*)-*N,N'*-Bis-(1-phenylethyl)-ethane-1,2-diamine (**30**).[52] 40.5 g (0.33 mol) (*S*)-(-)-*α*-phenylethylamine (**27**) was heated to 90°C. 1,2-dichloroethane (**28**) (9.0 ml (0.11 mol) was added dropwise over a period of 3 h. The mixture was stirred overnight at 90°C. The mixture was cooled to 60°C, 100 ml $KOH_{(aq)}$ (sat) was added and stirred while cooling to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x 75 ml). The combined organic layers were washed with brine and dried on Na_2SO_4. The organic solution was filtered and concentrated in vacuo. The excess (S)-(-)-*α*-phenylethylamine was removed by vacuum distillation. The crude product was purified by bulb-to-bulb distillation. The product was obtained as slightly yellow oil (bp. = 165-170°C / 0.6 mbar). Yield: 21.6 g (80.6 mmol; 73%). **$[\alpha]_D^{20}$** = -63.1° (c= 1.08, $CHCl_3$)[52]; **^{1}H-NMR** (300 MHz, $CDCl_3$):[52] δ 7.31-7.15 (m, 10H), 3.62 (q, *J* = 6.6 Hz, 2H), 2.49 (s, 4H), 1.44 (bs, 2H), 1.30 (d, *J* = 6.6 Hz, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[52] δ 145.8 (s), 128.3 (d), 126.7 (d), 126.5 (d), 58.1 (d), 47.3 (t), 24.4 (q); **HRMS** for $C_{18}H_{24}N_2$: calcd. 268.194 found 268.193.



(*R*,*R*)-*N*,*N*'-Bis-(1-phenylethyl)-propane-1,3-diamine (**31**).[52] Similar procedure as for **30**. Starting from 29.3 g (0.24 mol) (*R*)-(+)-*a*-phenylethylamine (**27**) and 8.5 ml (83.7 mmol) 1,3-dibromopropane (**29**), the product was obtained as a slightly yellow oil by bulb-to-bulb distillation (bp. = 171°C / 0.6 mbar). Yield: 18.6 g (66.0 mmol; 79%). **$[\alpha]_D^{20}$** = 59.0° (c= 1.16, $CHCl_3$);[52] **^{1}H-NMR** (300 MHz, $CDCl_3$):[52] δ 7.29-7.15 (m, 10H), 3.66 (q, *J* = 6.6 Hz, 2H), 2.50-2.37 (m, 4H), 1.56 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 6H); **^{13}C-NMR** (75.48 MHz, $CDCl_3$):[52] δ 145.8 (s), 128.3 (d), 126.7 (d), 126.5 (d), 58.4 (d), 46,4 (t), 30,4 (t), 24.4 (q); **HRMS** for $C_{19}H_{26}N_2$: calcd. 282.210 found 282.209.



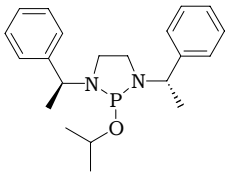
2-propyl phosphorodichlorite.[53] To a cooled (0°C) solution of 14.1 ml (0.15 mol) PCl_3 was added dropwise 8.1 ml (0.11 mol) 2-propanol. The mixture was warmed to room temperature and stirred overnight. The solution was distilled under reduced pressure. The product was obtained as a colorless liquid (bp. = 84°C; 18 mbar). Yield: 8.6 g (71 mmol; 67%). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.14-4.97 (m, 1H), 1.38 (d, *J* = 6.1 Hz, 6H); **^{31}P-NMR** (80.96 MHz, $CDCl_3$): δ 173.87; **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 74.8 (d), 22.5(q).



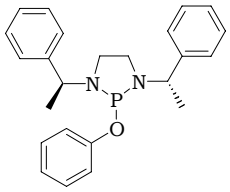
Phenyl phosphorodichlorite.[54] To 8.08 g (86.0 mmol) phenol was added dropwise 42 ml (0.48 mol) PCl_3. The solution was refluxed overnight. The excess PCl_3 was removed by distillation. The resulting crude liquid was purified by vacuum distillation. The product was obtained as a colorless liquid (bp. = 53°C; 0.6 mbar). Yield: 11.8 g (60.4 mmol; 77%). **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H); **^{31}P-NMR** (80.96 MHz, $CDCl_3$): δ 176.58; **^{13}C-NMR** (75.48 MHz, $CDCl_3$): δ 129.5 (d), 126.1 (d), 126.7 (d, J_{P-C} = 4.96).

General procedure for the synthesis of **32**-**35**:

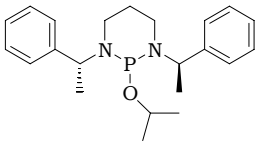
To a cooled solution of 5.33 mmol diamine and 1.31 ml (17.5 mmol) Et_3N in 15 ml ether (double Schlenk vessel) was added 5.33 mmol of the corresponding dichlorophosphite. The reaction mixture was allowed to warm slowly to room temperature and stirred for 2 h and then filtered. The clear solution was transferred under argon to another Schlenk vessel and concentrated under reduced pressure. The remaining yellow oils were used as obtained. The ligands were pure according to ^{31}P-NMR spectroscopy. In some cases traces of free amine (up to 5%) were observed in the ^{1}H- and ^{13}C-NMR spectra.



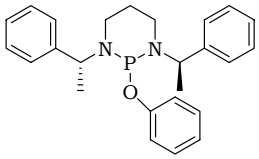
(*S,S*)-2-Isopropoxy-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphospholidine (**32**). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.38-7.15 (m, 10H), 4.41-4.37 (m, 1H), 4.21-4.19 (m, 1H), 4.18-4.06 (m,1H), 3.07-3.00 (m, 1H), 2.74-2.68 (m, 2H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$): δ 121.71; **^{13}C-NMR** (101.0 MHz, $CDCl_3$): δ 145.3 (d, J_{P-C} = 6.9 Hz), 144.8 (d, J_{P-C} = 4.6 Hz), 128,3 (d), 128,1 (d), 126.9 (d), 126.7 (d), 126.7 (d), 126.6 (d), 65.9 (dd, J_{P-C} = 17.6 Hz), 57.7 (dd, J_{P-C} = 15.3 Hz), 56.5 (dd, J_{P-C} = 23.0 Hz), 48.4 (dt, J_{P-C} = 8.4 Hz), 46.5 (dt, J_{P-C} = 9.2 Hz), 24.9 (dq, J_{P-C} = 2.3 Hz), 23.8 (dq, J_{P-C} = 15.3 Hz), 22.2 (dq, J_{P-C} = 13.0 Hz); **HRMS** for $C_{21}H_{29}NO_2P$: calcd. 356.201 found 356.202; **$[\alpha]_D^{20}$** = -7.5° (c= 1.01, $CHCl_3$).



(*S,S*)-2-Phenoxy-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphospholidine (**33**). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.40-7.21 (m, 12H), 7.04-6.98 (m, 3H), 4.50-4.46 (m, 1H), 4.24-4.21 (m, 1H), 3.21-3.14 (m,2H), 2.93-2.77 (m, 2H), 1.64 (d, *J* = 6.6 Hz, 3H), 1.63 (d, *J* = 5.5 Hz, 3H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$): δ 125.25; **^{13}C-NMR** (101.0 MHz, $CDCl_3$): δ 155.6 (s), 144.8 (d, J_{P-C} = 6.9 Hz), 144.2 (d, J_{P-C} = 4.70 Hz), 129.3 (d), 128.4 (d), 128.2 (d), 126.9 (d), 126.9 (d), 126.6 (d), 121.7 (d), 120.3 (d), 120.2 (d), 57.8 (dd, J_{P-C} = 14.6 Hz), 56.5 (dd, J_{P-C} = 21.5 Hz), 48.5 (dt, J_{P-C} = 8.4 Hz), 46.95 (dt, J_{P-C} = 9.2 Hz), 24.1 (dq, J_{P-C} = 16.1 Hz), 22.2 (dq, J_{P-C} = 13.8 Hz); **MS**: m/z 297; 100%; **$[\alpha]_D^{20}$** = -9.5° (c= 1.07, $CHCl_3$).



(*R,R*)-2-Isopropoxy-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphosphinane (**34**). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.44-7.20 (m, 10H), 4.59-4.54 (m, 1H), 4.27-4.23 (m, 1H), 4.11-4.04 (m,1H), 3.15-3.01 (m, 2H), 2.59-2.41 (m, 1H), 2.40-2.36 (m, 1H), 1.61 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1,51-1.43 (m, 2H), 1.27 (d, *J* = 5.9 Hz, 1.5 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$): δ 122.39; **^{13}C-NMR** (101.0 MHz, $CDCl_3$): δ 145.5 (d, J_{P-C} = 6.1), 144.3 (d, J_{P-C} = 10.0), 128,0 (d), 127.8 (d), 127.2 (d), 127.0 (d), 126.5 (d), 126.4 (d), 65.7 (dd, J_{P-C} = 16.9 Hz), 60.4 (dd, J_{P-C} = 29.1 Hz), 58.3 (dd, J_{P-C} = 3.9 Hz), 41.4 (dt, J_{P-C} = 4.8 Hz), 37.8 (dt, J_{P-C} = 4.6 Hz), 25.9 (t), 24.5 (dq, J_{P-C} = 3.8 Hz), 24.4 (dq, J_{P-C} = 3.1 Hz), 21.9 (dq, J_{P-C} = 18.4 Hz), 17.7 (dq, J_{P-C} = 6.1 Hz); **HRMS** for $C_{22}H_{31}N_2OP$: calcd. 370.217 found 370.216; **$[\alpha]_D^{20}$** = 20.5° (c= 1.31, $CHCl_3$).



(*R,R*)-2-Phenoxy-1,3-bis-(1-phenylethyl)-[1,3,2]diazaphosphinane (**35**). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.46-7.15 (m, 15H), 4.63-4.56 (m, 1H), 4.28-4.23 (m, 1H), 3.24-3.14 (m, 2H), 2.62-2.42 (m, 2H), 1.67-1.58 (m, 2H), 1.56 (dd, *J* = 7.0 Hz, 2.2 Hz, 3H), 1.43 (d, *J* = 7.0 Hz, 3H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$): δ 124.80; **^{13}C-NMR** (101.0 MHz, $CDCl_3$): δ 157.5 (s), 144.7 (d, J_{P-C} = 6.9), 143.6 (d, J_{P-C} = 10.7), 129.3 (d), 128.1 (d), 128.0 (d), 127.0 (d), 127.0 (d), 126.6 (d), 126.6 (d), 120.2 (d), 120.1 (d), 60.7 (dd, J_{P-C} = 30.7 Hz), 58.6 (dd, J_{P-C} = 41.4 Hz), 41.6 (dt, J_{P-C} = 4.6 Hz), 37.8 (dt, J_{P-C} = 4.6 Hz), 26.1 (t), 21.8 (dq, J_{P-C} = 19.2 Hz), 17.4 (dq, J_{P-C} = 5.4 Hz); **MS** (CI; 329 (M+H+); 347 (M+NH4+); **$[\alpha]_D^{20}$** = 6.6° (c= 1.00, $CHCl_3$).

Table 4.2: *E.e.*-determination methods of hydrogenation products of substrates **36**-**39**.

Entry	*Substrate*	*Method*	*Retention time (min)*	*Retention time (min)*
1	**36**	A	3.4 (R)	3.9 (S)
2	**37**	B	6.7 (R)	7.1 (S)
3	**38**	C	15.8 (S)	16.7 (R)
4	**39**	D	13.0 (S)	13.9 (R)

Method A: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12μm), 110°C
Method B: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.12μm), 160°C
Method C: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25μm), 140°C
Method D: CP Chiraldex G-TA from Altrack (30m x 0.25mm x 0.125μm), 80°C

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Chapter 5
Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Using a Mixed Ligand Approach

In this chapter the rhodium-catalyzed asymmetric hydrogenation of a series of unsaturated carboxylic acids is described, using a mixed ligand system of a chiral phosphoramidite and an achiral phosphine. Enantioselectivities up to 99% have been achieved.

Part of this chapter has been published:

Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4209-4212

5.1 Introduction

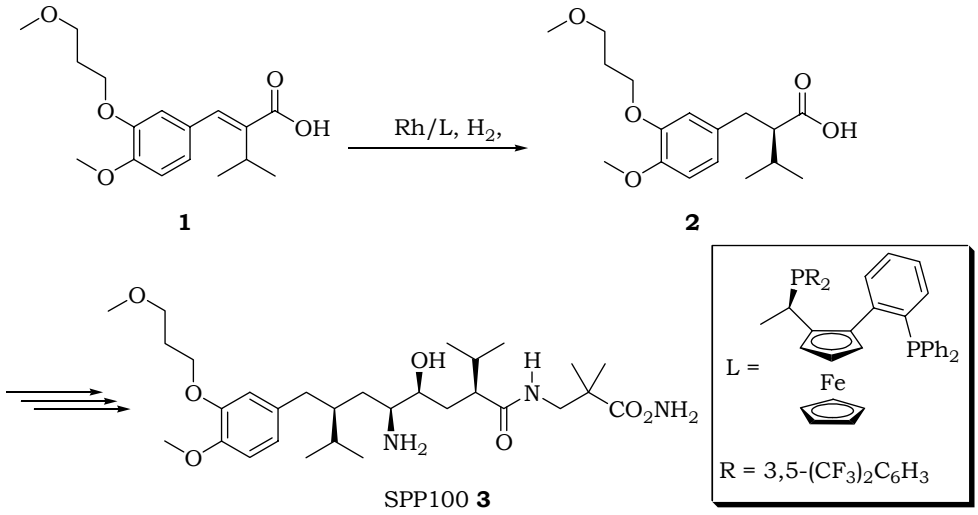
5.1.1 Monodentate ligands

The field of asymmetric hydrogenation has developed rapidly since the initial experiments by Knowles and Horner.[1] In the last 35 years thousands of ligands have been synthesized which, in combination with a variety of transition metals, can be employed in the hydrogenation of a broad range of prochiral olefins.[2] The most studied substrates in asymmetric hydrogenation are α-dehydroamino acids. Besides these, several other substrates have been examined such as: enamides, substituted itaconic acids, enol acetates, β-dehydroamino acids and unsaturated carboxylic acids.

Since Pringle,[3a] Feringa / De Vries / Minnaard[3b] and Reetz[3c] reported independently the use of monodentate ligands in the rhodium-catalyzed asymmetric hydrogenation, the number of reports on the use of monodentate ligands has been increasing exponentially.[4] The fact that two monodentate ligands are coordinating to Rh in the catalytic active species, was exploited by the groups of Reetz[5] and Feringa[6] to show that mixtures of (a)chiral monodentate ligands can be used to hydrogenate different substrates with enhanced selectivities (see chapter 1). This new strategy was also employed in the rhodium-catalyzed addition of boronic acids and the rhodium-catalyzed hydroformylation.[7]

5.1.2 Dihydrocinnamic acids

Dihydrocinnamic acids are an important class of compounds. They are key intermediates in the synthesis of a variety of bio-active compounds, including renin inhibitors,[8] γ-secretase inhibitors,[9] enkephalinase inhibitors,[10] endothelin receptor antagonists[11] or opioid antagonists.[12] These intermediates are not only interesting from a synthetic point of view, but also for industrial applications they can be very useful. For example, dihydrocinnamic acid **2**, which is an intermediate for renin inhibitor SPP100 (**3**), could be obtained on 39 mol scale (>12 kg) with 95% *e.e.*, after hydrogenation of cinnamic acid derivative **1** (see Scheme 5.1).[8a]



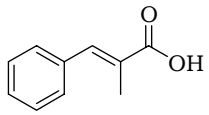
Scheme 5.1: Published asymmetric hydrogenation as part of the synthesis of Renin inhibitor SPP100 **3**.[8a]

5.1.3 Hydrogenation of unsaturated carboxylic acids

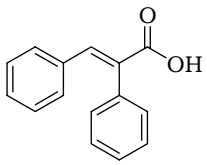
Relatively limited research has been done in the asymmetric hydrogenation of unsaturated carboxylic acids compared to for example α-amino acids. In the next two paragraphs an overview will be given of the relevant literature on the asymmetric hydrogenation of unsaturated carboxylic acids. The most frequently used benchmark substrates for this class of compounds are depicted in Figure 5.1.

5.1.3.1 Rhodium-catalyzed hydrogenations

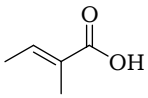
Yamashita and co-workers developed carbohydrate based monodentate phosphines and phosphonites. [13] These ligands induced modest enantioselectivities (65%) in the rhodium-catalyzed hydrogenation of tiglic acid (**6**). A carbohydrate based bidentate phosphine, synthesized by Johnson *et al.*, led to 61% *e.e.* in the hydrogenation of **4**.[14]



α-methylcinnamic acid (**4**)



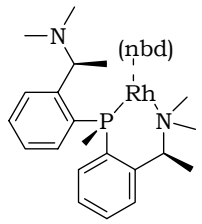
α-phenylcinnamic acid (**5**)



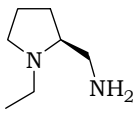
tiglic acid (**6**)

Figure 5.1: Benchmark unsaturated carboxylic acids.

Better results for the hydrogenation of unsaturated acids have been obtained with ferrocenyl-based ligands.[8a, 15] In the hydrogenation of **4**, enantioselectivities of 82% have been obtained when a Mandiphos derivative was used.[8a] A dramatic increase of enantioselectivity was observed when **4** was derivatized with a bulky *i*-propyl group on the *α*-position of the carboxylic acid moiety (Scheme 5.1).



7



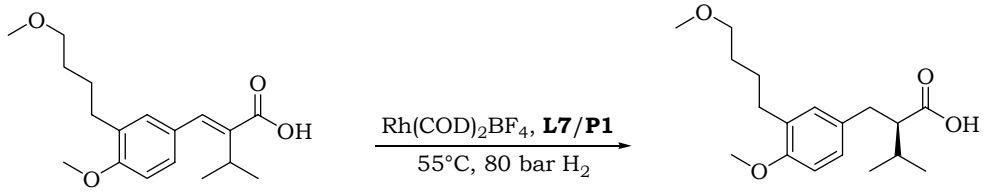
8

The best results obtained, so far, are with bidentate ligands containing an amine moiety, which participates in the coordination to the metal centre.[16] For example, complex **7**, developed by Yamagishi and co-workers, could hydrogenate substrates **4** and **6** in, respectively, 92% and 75% *e.e.*[16a,b] Thomas and co-workers developed a Rh-catalyst based on diamine **8**.[16d] This catalyst induced 93% *e.e.* in the hydrogenation of substrate **5**, at 77% conversion. An improvement of the enantioselectivity was observed when this diamine was anchored to silica. The ee could be increased up to 96% with this heterogeneous catalyst at 80% conversion.[16d]

Rhodium-catalyzed hydrogenations of unsaturated acids are in general slower compared to dehydroamino acids and harsher conditions are required, *e.g.* high pressures, high temperatures and long reaction times. For example, the hydrogenation of **5** with a Rh-complex of **8** was performed with 20 bar of hydrogen pressure and a reaction time of 24 hours at 40°C. Only 74% conversion was obtained, with a chemoselectivity of only 77% to the 2,3-diphenylpropionic acid. Variable amounts of other

products, such as 2,2- and 3,3-diphenylpropionic acids, were found as well in this reaction.

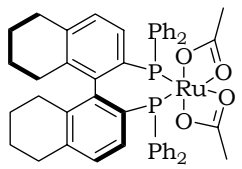
An interesting new development occurred when J. Boogers at DSM was screening catalyst for the asymmetric hydrogenation of **1**. He found that addition of triarylphosphines not only increased the enantioselectivity in the Rh/MonoPhos (**L1**) catalyzed hydrogenation of **1**, but also had the effect of enhancing the rate. This eventually has led to a process for **2** as depicted in Scheme 5.2.[17]



1 **2** 90% *e.e.*

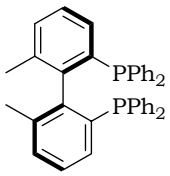
Scheme 5.2: Asymmetric hydrogenation of **1** using a mixed ligand base catalyst.[17]

5.1.3.2 Ruthenium-catalyzed hydrogenations

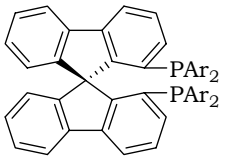


9

The ruthenium-catalyzed hydrogenation of tiglic acid (**6**) with (functionalized) BINAP complexes has been extensively studied. [18] Excellent enantioselectivities were obtained under relatively mild reaction conditions. For example, complex **9**, based on 8H-BINAP ligand, hydrogenated **6** with an enantiomeric excess of 97%, in 20 hours with 1.5 bar of H_2 pressure.[18h] Furthermore, **9** also performed well in the hydrogenation of substrates **4** and **5**. The reduced products could be obtained in 89% and 74% *e.e.*, respectively. Higher pressures and longer reaction times were needed for substrate **5**, however (27 bar and 61 h).



BIPHEMP **10**



11 a) Ar = 3,5-$Me_2C_6H_3$
b) Ar = 3,4,5-$Me_3C_6H_2$

In addition to the BINAP systems, a variety of other ruthenium complexes has been studied. [19] Almost perfect stereo control was obtained in the hydrogenation of **6** with biphenyl-based ligand **10**,[19d] and spirofluorene-based ligand **11a**.[19i] On the other hand, ligand **11b** gave good *e.e.'s* in the hydrogenation of substrate **4**.

5.1.4 Goal of this research

Chiral carboxylic acids are important building blocks for a range of bio-active compounds (see §5.1.2). The majority of ligands which are successful in the Rh- or Ru-catalyzed hydrogenation of unsaturated carboxylic acids, is bidentate in nature. In general, a lengthy synthesis is required to obtain these ligands, which makes it difficult to modify them. Alternatively, monodentate phosphoramidites can be synthesized in one or two steps. The easy synthesis makes it possible to use these ligands in a high throughput screening, as developed by DSM and in our group. [20]

The goal of this research was to extend the scope and further investigate the mixed ligand system that was originally found at DSM for the rhodium-catalyzed asymmetric hydrogenation of *a,β*-unsaturated carboxylic acids.

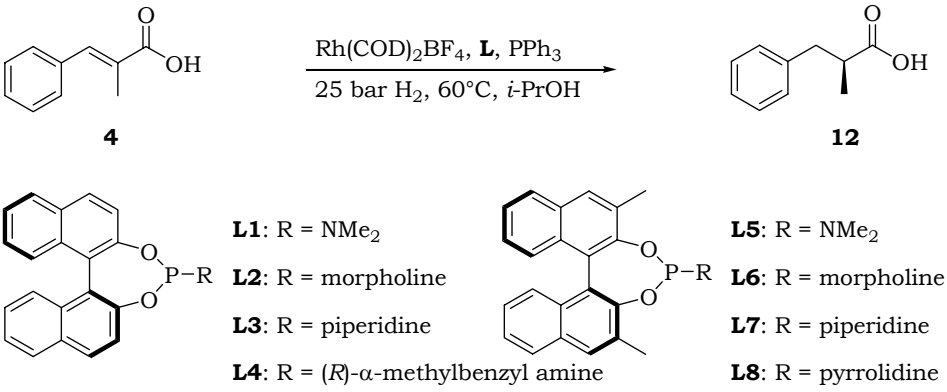
5.2 Reaction conditions

5.2.1 Initial Screening and ligand optimization

An initial screening of monodentate phosphoramidites ligands in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**4**) gave rather poor results (Table 5.1, odd entries). Addition of an equivalent of *achiral* triphenylphosphine, *i.e.* employing a 2:1 ratio of phosphoramidite : triphenylphosphine, gave a dramatic increase in

conversion and in enantioselectivity, compared to the corresponding homo-complexes of the phosphoramidites (Table 5.1, even entries).

Table 5.1: Screening of phosphoramidites in the rhodium-catalyzed asymmetric hydrogenation of **4**.[a,b]



L1: R = NMe_2
L2: R = morpholine
L3: R = piperidine
L4: R = (*R*)-α-methylbenzyl amine
L5: R = NMe_2
L6: R = morpholine
L7: R = piperidine
L8: R = pyrrolidine

Entry	*Ligand*	*Conversion*	*E.e.*[c]
1	**L1**	43	8
2	**L1** + PPh_3	100	43
3	**L2**	72	0
4	**L2** + PPh_3	100	55
5	**L3**	76	0
6	**L3** + PPh_3	100	63
7	**L4**	91	0
8	**L4** + PPh_3	100	37
9	**L5**	91	10
10	**L5** + PPh_3	100	80
11	**L6**	82	3
12	**L6** + PPh_3	100	80
13	**L7**	81	2
14	**L7** + PPh_3	100	85
15	**L8**	86	16
16	**L8** + PPh_3	100	76

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 of mmol phosphoramidite and 0.01 of mmol PPh_3 (b) Reactions were run for 5 h. (c) *E.e.*'s were determined by chiral GC after conversion of product to the corresponding methyl ester (for details see experimental section) (d) In all cases the R enantiomer of the ligands led to the S enantiomer of product.

For example, the use of **L3** in combination with triphenylphosphine resulted in an enhancement of the conversion from 72% to 100% and *e.e.* from 0% to 63% (entries 5 and 6). It was observed that phosphoramidites based on 3,3'-dimethyl-BINOL induced distinctly higher *e.e.'s* than the phosphoramidites based on BINOL (entries 1-8 vs. 9-16). The use of piperidine-based phosphoramidite **L7** further improved the enantioselectivities. For the catalyst based on **L7** the addition of triphenylphosphine increased the *e.e.* from 2% to 85% (entries 13 and 14).

5.2.2 Optimization of solvent, temperature and pressure

5.2.2.1 Solvent effect

Screening of a series of protic solvents in the rhodium-catalyzed hydrogenation of *α*-methylcinnamic acid (**4**) showed that *i*-propanol is the best solvent for these hydrogenations, although the results with methanol and ethanol were almost the same (entries 1-3, Table 5.2). Furthermore, addition of water as a co-solvent with *i*-propanol gave a slight increase in *e.e.* (entries 4-7). In the presence of water at higher temperatures the ligands were stable, as long as they were bound to rhodium. Similar observations were made in the rhodium-catalyzed addition of boronic acid to enones.[21] Free phosphoramidites, on the other hand, hydrolyze in the presence of water at higher temperatures within 5 hours.[22]

5.2.2.2 Temperature effect

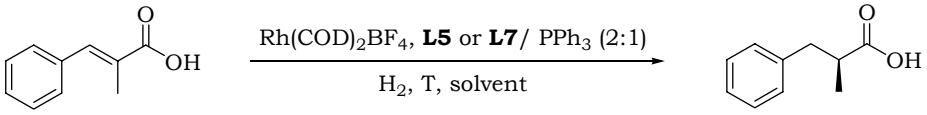
Decreasing the temperature from 60°C to 30°C led to an increase of enantioselectivity from 81% to 84% (entries 5 and 8-10, Table 5.2). The *e.e.* stayed constant when the temperature was lowered to 25°C, but in this case no full conversion was obtained.

5.2.2.3 Pressure effect

The effect of hydrogen pressure was examined under optimized conditions, *i.e.* ligand **L7**, a temperature of 30°C and a 4:1 mixture of *i*-

propanol and water as solvent. Lowering the pressure from 25 to 1 bar led to a decrease in enantioselectivity. No full conversion was obtained at 1 bar of hydrogen pressure. The drop in selectivity is attributed to a combination of a lower reaction rate and partial decomposition of the catalyst. In some cases rhodium black formation was observed, which causes an undesired and unselective side reaction.

Table 5.2: Screening of solvent, temperature and pressure in the rhodium-catalyzed asymmetric hydrogenation of **4**.[a,b]



4 **12**

Entry	*Ligand*	*Solvent*	*Temperature (°C)*	*Pressure (bar)*	*E.e.*[c,d] (%)
1	**L5**	MeOH	60	25	79
2	**L5**	EtOH	60	25	79
3	**L5**	*i*-PrOH	60	25	80
4	**L5**	*i*-PrOH / 10% H_2O	60	25	80
5	**L5**	*i*-PrOH / 20% H_2O	60	25	81
6	**L5**	*i*-PrOH / 30% H_2O	60	25	81
7	**L5**	*i*-PrOH / 40% H_2O	60	25	81
8	**L5**	*i*-PrOH / 20% H_2O	50	25	82
9	**L5**	*i*-PrOH / 20% H_2O	40	25	83
10	**L5**	*i*-PrOH / 20% H_2O	30	25	84
11	**L5**	*i*-PrOH / 20% H_2O	25	25	84 (93)
12	**L7**	*i*-PrOH / 20% H_2O	30	25	88
13	**L7**	*i*-PrOH / 20% H_2O	30	20	88
14	**L7**	*i*-PrOH / 20% H_2O	30	15	85
15	**L7**	*i*-PrOH / 20% H_2O	30	10	84
16	**L7**	*i*-PrOH / 20% H_2O	30	5	81
17	**L7**	*i*-PrOH / 20% H_2O	30	1	79 (87)

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 of mmol $Rh(COD)_2BF_4$, 0.02 mmol of phosphoramidite and 0.01 of mmol PPh_3 (b) Reactions were run for 16 h (c) *E.e.*'s were determined by chiral GC after conversion of the product to the corresponding methyl ester (for details see experimental section); full conversion was obtained otherwise indicated in brackets (d) In all cases the *R* enantiomer of ligand led to the *S* enantiomer of products.

5.2.3 Phosphine optimization

5.2.3.1 Ratio of phosphoramidite / phosphine

A rather poor *e.e.* of 10% was obtained in the hydrogenation of **4** with a **L5** to $Rh(COD)_2BF_4$ ratio of 2. Also in the case of 3 equivalents of **L5** the selectivity remained low. Addition of 1 equivalent of PPh_3, relative to **L5**, increased the *e.e.* dramatically (entries 1-3, Table 5.3). The amount of phosphine could be decreased to 0.5 equivalent with respect to **L5** (**L5** : PPh_3 = 4:1) without any loss of selectivity. On the other hand, further reduction of the phosphine amount to 0.2 equivalents led to a decrease in *e.e.* (entries 3-5). Nevertheless, addition of even a small amount of *achiral* PPh_3 increases the *e.e.* dramatically compared to the use of solely the *chiral* phosphoramidite **L5**. Using 1:1 ratios of **L5** and PPh_3 gave slightly lower enantioselectivities (entries 3, 6 and 7). Surprisingly, the hydrogenation even proceeded when 4 equivalents of ligand were used compared to the rhodium precursor. Earlier studies revealed that the addition of 4 equivalents of a monodentate phosphoramidite (MonoPhos™) to $Rh(COD)_2BF_4$ forms an unreactive complex with 4 ligands coordinated to the Rh centre.[4] Also the use of an 1:2 ratio of **L5** to PPh_3 diminished the enantioselectivity (entries 3 and 8). The use of the corresponding methyl ester of **4** gave a higher *e.e.* than **4** itself when only **L5** was applied as a ligand. Addition of an equivalent of PPh_3 resulted in a nearly racemic mixture (entries 1, 9 and 10). A similar effect, in which the free acid performs better than the methyl ester, was observed by Yamada *et al.*[16] They ascribed this effect to the participation of an electrostatic interaction between their ligand and the substrate (see picture). In our case it is probably due to the fact that the free acid coordinates better to the rhodium, than the methyl ester. This second coordination is well-known (see also §1.5.5) and proves to be important for enantiodiscrimination.[23] Another remarkable effect was observed; although the same enantiomer of **L5** was used, the configuration of the product changed when the methyl ester was used instead of the acid.

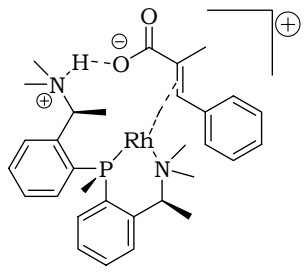
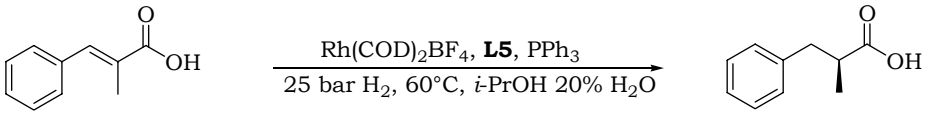


Table 5.3: Variation of the phosphoramidite / phosphine ratio in the rhodium-catalyzed asymmetric hydrogenation of **4**.[a,b]



4 **12**

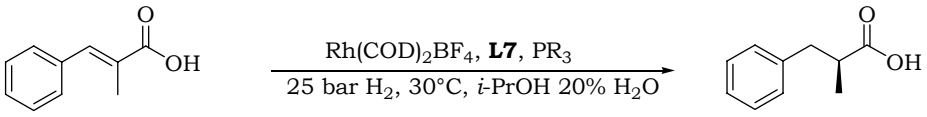
Entry	*Mol % **L5***	*Mol % PPh_3*	*E.e.*[c,d]
1	2	0	10
2	3	0	14
3	2	1	81
4	2	0.5	81
5	2	0.2	70
6	2	2	77
7	1	1	77
8	1	2	73
9[e]	2	0	30[f]
10[e]	2	1	4

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 mmol of $Rh(COD)_2BF_4$, phosphoramidite and PPh_3 (b) Reactions were run for 16 h (c) *E.e.'s* were determined by chiral GC after conversion of product to the corresponding methyl ester (for details see experimental section), full conversion was obtained otherwise indicated in brackets (d) In all cases the *R* enantiomer of ligand led to the *S* enantiomer of products (e) Methyl ester was used (f) *R* enantiomer of ligand gave *R* enantiomer of product.

5.2.3.2 Structural variation in the phosphine ligand

A screening of structurally different phosphines was performed to achieve further optimization of the reaction outcome. A variety of achiral alkyl phosphines and substituted aryl phosphines was tested in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**4**) using **L7** (Table 5.4). The reactions were performed with 1 and 0.5 equivalent of phosphine compared to **L7**.

Table 5.4: Screening of achiral phosphines in the rhodium-catalyzed asymmetric hydrogenation of **4**.[a,b]



4 **12**

Entry	*R*	*1 eq. PR3*		*0.5 eq. PR3*	
		E.e.[c,d]	*T.O.F.*[e]	*E.e.*	*T.O.F.*[e]
1	-	16 (34)	2	-	-
2	Ph (**P1**)	88	46	88	78
3	*o*-tolyl (**P2**)	97	33	95	20
4	*m*-tolyl (**P3**)	87	69	87	78
5	*p*-tolyl (**P4**)	86	61	86	81
6	xylyl (**P5**)	89	92	89	50
7	mesityl (**P6**)	33 (55)	3	30 (56)	3
8	*m*-ClPh (**P7**)	89	46	87	78
9	*p*-ClPh (**P8**)	90	18	86	19
10	cyclohexyl (**P9**)	87	28	86	26
11	*n*-butyl (**P10**)	67	17	56 (84)	5
12	*t*-butyl (**P11**)	13 (39)	2	4 (27)	1.4

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 mmol of phosphoramidite and 0.01 or 0.005 mmol of PPh_3 (b) Reactions were run for 16 h (c) *E.e.*'s were determined by chiral GC after conversion of product to the corresponding methyl ester (for details see experimental section), full conversion was obtained unless indicated in brackets (d) In all cases the *R* enantiomer of ligand led to the *S* enantiomer of products (e) T.O.F. in mol (substrate) mol^{-1} (catalyst) h^{-1}.

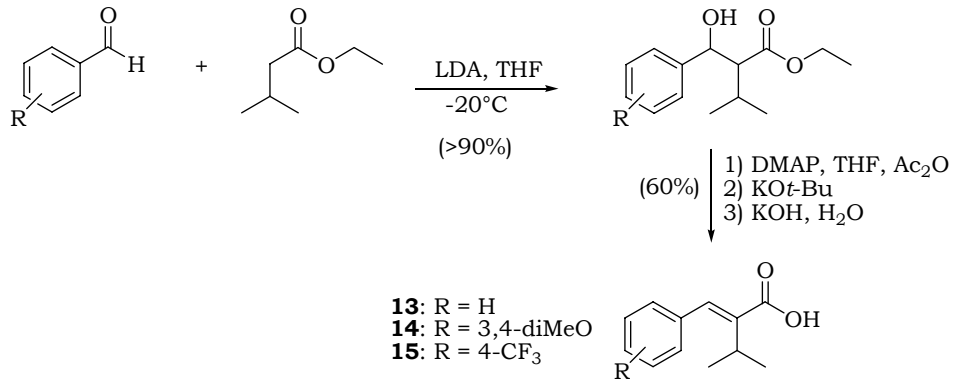
In most cases there was hardly any difference in *e.e.* between the use of 0.5 or 1 equivalent of phosphine. Only in a few cases slightly higher selectivities were obtained with 1 equivalent of achiral ligand. Substitution at the ortho position of triphenylphosphine increased the *e.e.* significantly (entries 2 and 3, Table 5.4), whereas substitution at the meta- or para-position had hardly any influence on the enantioselectivity (compare entries 2, 4, 5, 8 and 9). Linear or branched alkyl phosphines showed a decrease in rate and enantioselectivity compared to tricyclohexylphosphine **P9** (entries 10, 11, 12).

Electron donating or withdrawing substituents on the arylphosphines had no influence on the *e.e.* (compare entries 2 with 4,5 and 8,9). While reactions were in general complete after 2 h, incomplete conversions were

obtained with the sterically hindered phosphines **P6** and **P11** after 16 h (entries 7, 12). In these cases not only the rate of the hydrogenations decreased, but also the enantioselectivities dropped dramatically. In most cases, higher T.O.F.'s were observed when 1 equivalent of phosphine was used compared to 0.5 equivalent. As mentioned before, besides bulky phosphines, alkyl phosphines also induced lower T.O.F.'s compared to the aryl phosphines (entries 2, 10-12). Introduction of an electron withdrawing chloro substituent decreased the T.O.F. (entries 2, 8, 9) On the other hand, introduction of alkyl groups on the aromatic ring increased the T.O.F. (entries 2-7). The highest T.O.F.'s were observed with meta substituted aryl phosphines (entries 2, 4, 6 and 8).

5.2.4 Broadening the scope of substrates

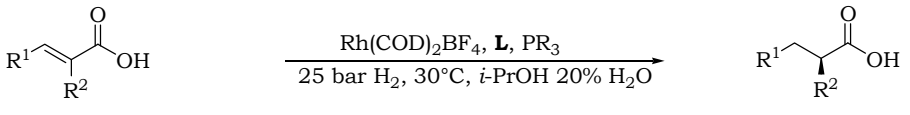
The scope of substrates was broadened by studying a number of disubstituted acrylic acids (Scheme 5-2). In addition to the commercially available benchmark substrates **5** and **6**, some substituted *α-i*-propylcinnamic acids were studied. These substrates are not commercially available and had to be synthesized. The synthesis is depicted in Scheme 5.3.[38]



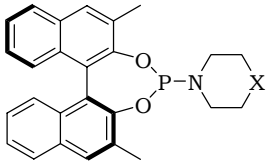
Scheme 5.3: Synthesis of substrates **20**-**22**.

A straightforward Claisen condensation followed by dehydration and saponification gave the desired products in >50% yield over two steps. In all cases solely products with an *E*-configuration were isolated, which was

Table 5.5: Rhodium-catalyzed hydrogenation of substituted acrylic acids.[a,b]



5: R^1 = Ph, R^2 = Ph
6: R^1 = Me, R^2 = Me
20: R^1 = Ph, R^2 = *i*-Pr
21: R^1 = 3,4-$(MeO)_2$Ph, R^2 = *i*-Pr
22: R^1 = 4-CF_3Ph, R^2 = *i*-Pr



L6: X = O
L7: X = CH_2

23: R^1 = Ph, R^2 = Ph
24: R^1 = Me, R^2 = Me
25: R^1 = Ph, R^2 = *i*-Pr
26: R^1 = 3,4-$(MeO)_2$Ph, R^2 = *i*-Pr
27: R^1 = 4-CF_3Ph, R^2 = *i*-Pr

Entry	*Substrate*	*Product*	***P***	*E.e.*[c,d] (**L6**)	*T.O.F.*[e] (**L6**)	*E.e.*[c,d] (**L7**)	*T.O.F.*[e] (**L7**)
1[f]	**5**	**23**	**P1**	87	N.D.	86	N.D.
2[f]	**5**	**23**	**P2**	92	N.D.	95	N.D.
3[f]	**5**	**23**	**P3**	72	N.D.	81	N.D.
4[f]	**5**	**23**	**P4**	76	N.D.	80	N.D.
5	**6**	**24**	**P1**	87	10	78	13
6	**6**	**24**	**P2**	73 (39)	2.0	84	10
7	**6**	**24**	**P3**	87	8.0	79	46
8	**6**	**24**	**P4**	86	10	76	16
9	**20**	**25**	**P1**	96	9.0	95	35
10	**20**	**25**	**P2**	86 (30)	2.0	99	22
11	**20**	**25**	**P3**	96	10	95	22
12	**20**	**25**	**P4**	96	12	93	13
13	**21**	**26**	**P1**	-	-	92	17
14	**21**	**26**	**P2**	-	-	90 (40)	3.0
15	**21**	**26**	**P3**	-	-	91	15
16	**21**	**26**	**P4**	-	-	89	15
17	**22**	**27**	**P1**	-	-	94	18
18	**22**	**27**	**P2**	-	-	94	6
19	**22**	**27**	**P3**	-	-	95	18
20	**22**	**27**	**P4**	-	-	93	24

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 mmol of phosphoramidite and 0.01 mmol of phosphine (b) Reactions were run for 16 h (c) *E.e.'s* were determined by chiral GC or HPLC, full conversion was obtained unless indicated otherwise (d) In all cases the *S* enantiomer of ligand led to the *S* enantiomer of products[24] (e) T.O.F. in mol (substrate) mol^{-1} (catalyst) h^{-1} (f) Reactions were performed at 60°C.

confirmed for two substrates by X-ray analysis (see §5.6). The substrates were tested under optimized conditions, *i.e.* 25 bar H_2, 30°C and *i*-PrOH : H_2O (4:1) as solvent and **L6** or **L7** in combination with phosphine **P1**-**P4** as ligands (**L**:**P** = 2:1) (Table 5.5).

In all cases, full conversions of the substrates were obtained with high to excellent *e.e.'s*. With the exception of substrate **6**, best results were obtained with a combination of **L7** and a phosphine (Table 5.5). In cases were R^1 is an aromatic group the enantioselectivity is higher than when R^1 is an alkyl group as in tiglic acid **6** (compare Table 5.4, entries 2-5 with Table 5.5 entries 5-8). Electron donating as well as electron withdrawing substituents at the aromatic moiety hardly affected the enantioselectivity (entries 9-20, Table 5.5). The size of R^2 also has hardly any influence on the enantioselectivities. Enantiomeric excesses of ≥ 95% for **12**, **16** and **18** could be obtained by fine tuning of the phosphine-phosphoramidite combination (Table 5.4 entry 3, Table 5.5 entries 2 and 10).

In general, using **L7** the T.O.F.'s were higher than when **L6** was used. In addition to the enantioselectivities, the T.O.F.'s for tiglic acid (**6**) were also lower than for α-methylcinnamic acid (**4**) (Table 5.4 entries 2-5, Table 5.5 entries 5-8). Introduction of a bulky *i*-propyl group at R^2 decreased the T.O.F. (Table 5.4 entries 2-5, Table 5.5 entries 9-20), as well as the introduction of electron withdrawing or electron donating groups on the aromatic moiety (Table 5.5, entries 9-12 vs. 13-20).

5.3 ^{31}P-NMR experiments

Although the initial formed complexes are not the active catalytic species, they can give insight into a possible structure of this species. ^{31}P-NMR spectroscopy was used to elucidate the structure of the formed complexes in our mixed ligand system. Three different complexes are formed on mixing the rhodium precursor with phosphoramidite **L7** and triphenylphosphine **P1** (Figure 5.2).[25] Next to the homo-complexes $\mathbf{RL_2}$ and $\mathbf{RP_2}$, hetero-complex **RLP** will be formed. Both homo-complexes will give a doublet, showing only a phosphorus-rhodium coupling.[26] The hetero-complex will show two signals, one arising from the triphenylphosphine and one from the phosphoramidite. Both signals will appear as a double

doublet, showing a rhodium-phosphorus as well as a phosphorus-phosphorus coupling.

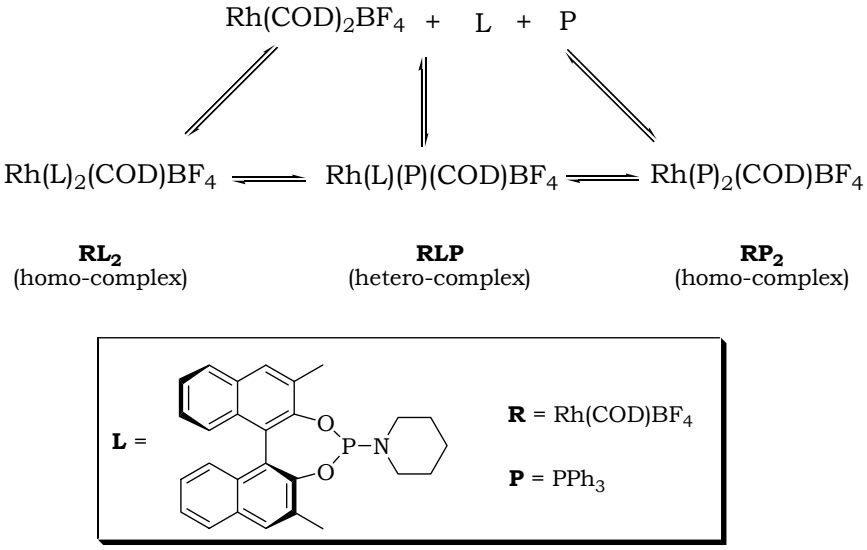


Figure 5.2: Equilibria in Rh / ligand complex formation.

Figure 5.3 shows the ^{31}P signals which can be attributed to phosphoramidite **L7** in complexes formed with a 1:1 (a) and a 1:2 (b) ratio of **L7** and **P1**. Spectrum (a) in Figure 5.3 shows the presence of mainly the hetero-complex (double doublet at 135.8 ppm) and only a small trace of homo-complex $\mathbf{RL_2}$ (doublet at 132.7 ppm). In a 1:2:1 mixture of $Rh(COD)_2BF_4$, **L7** and **P1** (Figure 5.3b), the amount of hetero-complex decreases and the amount of homo-complex increases. Furthermore, a substantial amount of free phosphoramidite (**L7**) (singlet at 142.7 ppm) is present. This is not surprising since an excess of **L7** has been used (entries 5 and 6, Table 5.6).

Figure 5.4 shows the signals which are attributed to **P1** in the former mentioned complexes. In a 1:1 mixture of **L7** : **P1** both the homo-complex $\mathbf{RP_2}$ (doublet at 25.9 ppm) and the hetero-complex **RLP** (double doublet at 30.6 ppm) can be observed (Figure 5.4a). On the other hand, a 2:1 mixture of **L7**:**P1** shows only the presents of the hetero-complex and a trace of triphenylphosphine oxide (entries 5 and 6, Table 5.6). The absence of detectable amounts of homo-complex $\mathbf{RP_2}$ in a 2:1 mixture explains the higher *e.e.* compared to a 1:1 mixture (entries 3 and 7, Table 5.3).

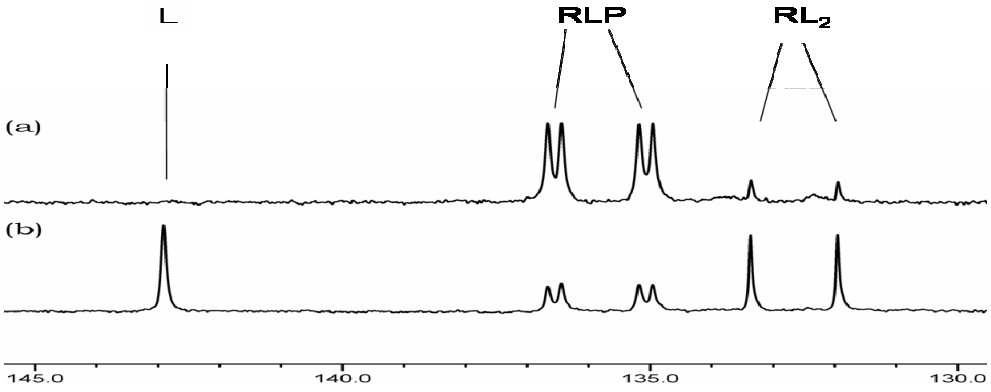


Figure 5.3: ^{31}P-NMR of **L7** in $Rh(COD)_2BF_4$ / **L7** / **P1** mixtures; (a) 1:1:1 ratio (b) 1:2:1 ratio.

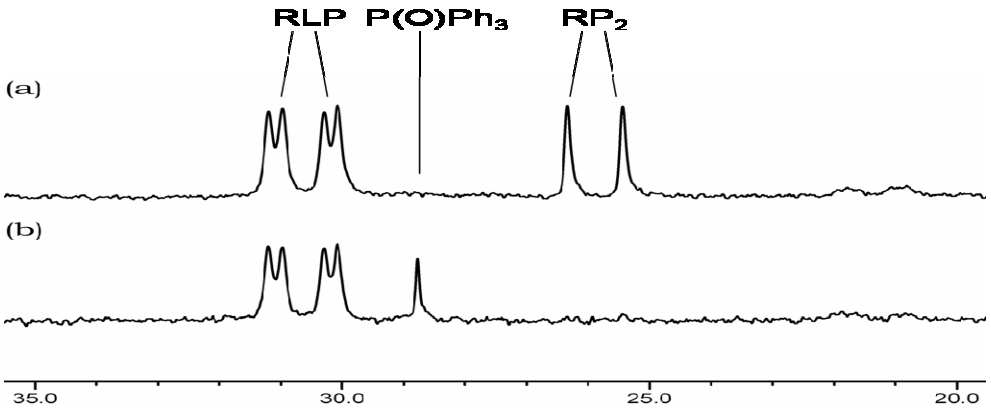


Figure 5.4: ^{31}P-NMR of **P1** in $Rh(COD)_2BF_4$ / **L7** / **P1** mixtures; (a) 1:1:1 ratio (b) 1:2:1 ratio.

In addition to the selective reaction by hetero-complex **RLP** a competing non-selective reaction by homo-complex **RP_2** takes place. Since there is only a slight drop in selectivity, this indicates that the rate of reaction of the hetero-complex **RLP** is much higher than the rate of reaction of the homo-complex **RP_2** (entries 3 and 7, Table 5.3).[27] Furthermore, this also indicates that the hetero-complex **RLP** is much faster than the homo-complex **RL_2**.

Table 5.6 shows the percentage of different complexes in a series of experiments. In a mixture with a 2:1 ratio of **L7** : **P1** approximately 40% of the Rh-ligand complex is present as a hetero-complex, while in a 1:1 mixture the hetero-complex is present in about 70% (entries 5 and 6). Mixing homo-complexes **RL_2** and **RP_2** shows a very fast exchange of ligands. In this case, an equilibrium is obtained which is stable over hours and which gives the same ratios of complexes as obtained when $Rh(COD)_2BF_4$, **L7** and **P1** are mixed in a 1:2:1 ratio (compare entries 6 and 7). In both entries some other species were formed, which are probably complexes with only 1 ligand coordinated to the rhodium. The process of exchange proceeds most likely via a dissociative kind of mechanism, since there is no free ligand present in both mixtures containing only homo-complexes. Dissociative mechanisms have been reported before in ligand exchange processes of rhodium complexes.[28]

Table 5.6: Ratio's of complexes.[a]

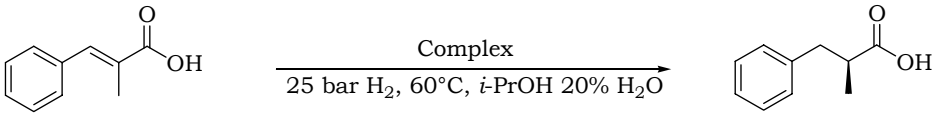
Entry	*Mixture*[b]	*T*[c]	**L7**	**RL_2**	**P1**	**RP_2**	**RLP**	**LO**[d]	**PO**[e]
1	**L7**	5 min	100	-	-	-	-	-	-
2	**Rh** + **2L7**	5 min	-	100	-	-	-	-	-
3	**P1**	5 min	-	-	100	-	-	-	-
4	**Rh** + **2P1**	5 min	-	-	-	100	-	-	-
5	**Rh** + **2L7** + **P1**	1 h	27	19	5	-	39	4	6
6[f]	**Rh** + **L7** + **P1**	1 h	-	5	-	14	69	-	-
7[f]	(**Rh** + **2L7**) + (**Rh** + **2P1**)	5 min	-	11	-	16	73	-	-
		1 h	-	5	-	12	65	-	-
		2 h	-	6	-	10	68	-	-
8	(**Rh** + **2L7**) + **P1**	5 min	38	13	14	-	35	-	-
		1 h	34	13	10	1	34	3	5
9	(**Rh** + **2P1**) + **L7**	5 min	7	-	36	14	37	-	6
		1 h	7	-	29	16	37	-	12

(a) Amounts are given in percentages (b) **Rh** = $Rh(COD)_2BF_4$ (c) Time were the spectra have been recorded (d) Hydrolyzed **L7** (e) Triphenylphosphine oxide (f) Some unidentified complexes were present, probably complexes with only one P-ligand coordinated to Rh.

Also in the cases when a homo-complex was mixed with an equivalent of the other P-ligand a fast exchange of ligands was observed (entries 8 and 9). Again, a fast equilibrium was established which did not change in time. In both cases about 35% of hetero-complex was formed, as was observed before in a 2:1 mixture of **L7** and **P1** (entries 5,8 and 9). In those mixtures where 3 equivalents of ligands were used compared to the rhodium precursor, small amounts of hydrolyzed phosphoramidite and/or oxidized triphenylphosphine were observed. This indicates that ligands which are not complexed to the metal are more prone to hydrolysis or oxidation than ligands which are complexed. Similar results have been found in the rhodium-catalyzed boronic acid additions.[21]

These mixtures of complexes were used in a range of hydrogenation experiments. The results are depicted in Table 5.7.

Table 5.7: Hydrogenation experiments with a variety of complexes.[a,b]



4 **12**

Entry	*Mixtures*[c]	*E.e.*[d,e]
1	**Rh** + **2L7** + **P1** (*in situ*)	85
2	**Rh** + **2L7** + **P1** (pre-formed)	85
3	**Rh** + **L7** + **P1** (pre-formed)	83
4	**Rh** + **2L7** (pre-formed)	11
5	**Rh** + **2P1** (pre-formed)	-
6	(**Rh** + **2L7** + **P1**) (pre-formed) + **P1**	85
7[f]	**Rh** + **2L7** + **P1** (*in situ*)	83

(a) Reaction conditions: 1 mmol of substrate in 4 ml of solvent with 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 mmol of phosphoramidite and 0.01 mmol of phosphine or 1 mol % of preformed catalyst (b) Reactions were run for 16 h (c) *In situ* mixtures were formed by mixing ligands, $Rh(COD)_2BF_4$ and substrate in reaction vial and adding solvent. The obtained yellow solution was used in hydrogenation experiment. Pre-formed mixtures were formed by dissolving 1 eq. of $Rh(COD)_2BF_4$ and 2 or 3 eq. of appropriate ligand(s) in CH_2Cl_2. The mixture was stirred for 15 min and the CH_2Cl_2 was evaporated. The obtained yellow solid was used as obtained (d) *E.e.'s* were determined by chiral GC or HPLC, full conversion was obtained unless indicated otherwise (e) In all cases the *S* enantiomer of ligand led to the *S* enantiomer of products[29] (f) Na-salt of acid was used.

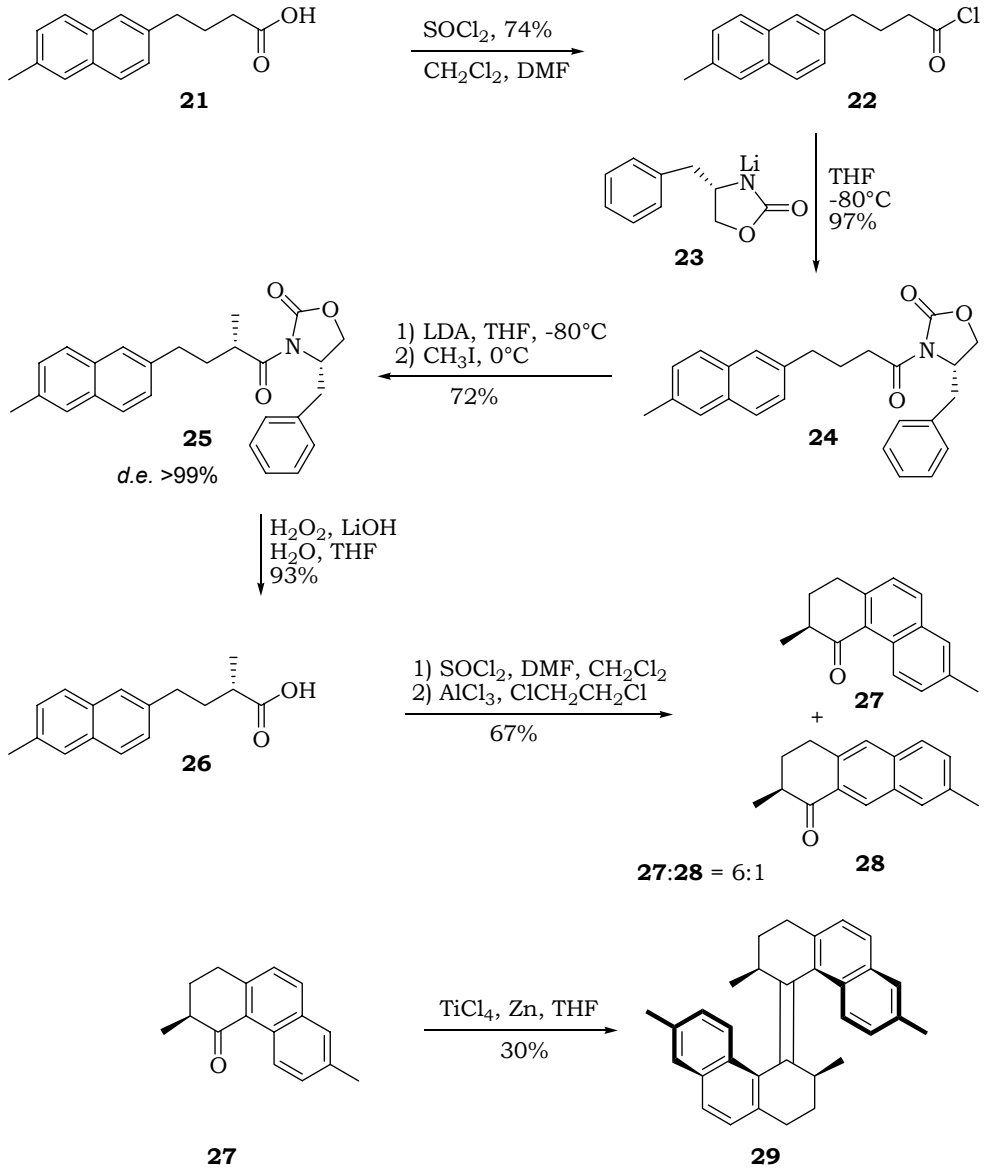
Entries 1 and 2 show, that there is no difference regarding the enantioselectivity in using an *in situ* formed complex or a preformed complex. As was observed before, application of a 1:1 mixture of **L7**:**P1** shows a slight decrease in *e.e.* (entry 3). The homo-complex $\mathbf{RL_2}$ gave a poor *e.e.* (entry 4). Identical enantioselectivities as for entries 1 and 2 were obtained when homo-complex $\mathbf{RL_2}$ was used with an extra equivalent of **P1**, which supports the results obtained from the ^{31}P-NMR experiments. Using the Na-salt of the substrate showed just a slight decrease in *e.e.* (entry 7).

The results obtained from the ^{31}P-NMR experiments and the hydrogenation with different complexes clearly shows that exchange of ligands takes place. This is contradictory to earlier results obtained from UV and NMR experiments.[30] Furthermore, the choice of MonoPhos™ (**L1**) to perform these initial experiments might have been unfortunate, since the behavior of MonoPhos™ (**L1**) is not completely representative for the class of BINOL-based phosphoramidites.[31]

5.4 Applications

As already mentioned in the introduction, chiral substituted carboxylic acids are important building blocks for a range of bioactive compounds. Not only in this field, but also in nanotechnology the building blocks have proven to be important. In 1999, Feringa and co-workers reported the first unidirectional molecular motor, which was based on a sterically overcrowded alkene.[32] The motors were synthesized as racemates and a tedious separation of the enantiomers by chiral preparative HPLC was required afterwards to obtain the enantiomerically pure motors.

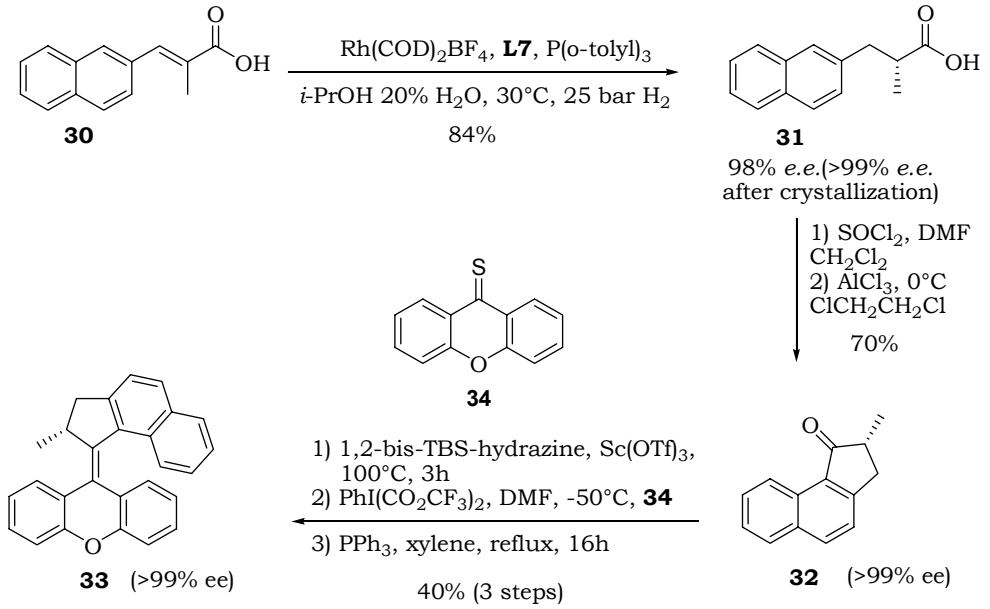
An asymmetric synthesis, based on a diastereoselective alkylation using the Evans protocol was developed, to avoid the time consuming and costly resolution step (Scheme 5.4).[33] Alkylation of oxazolidinone **24**, which could be obtained by amidation of **22** with **23**, gave **25** in 72% yield with perfect stereocontrol. Cyclic ketone **27** was obtained after deprotection of **25**, followed by a Friedel-Crafts acylation, without racemization. A titanium tetrachloride and zinc powder mediated McMurry coupling gave enantiomerically pure sterically overcrowded alkene **29** in solely the *E*-configuration.



Scheme 5.4: Stereoselective synthesis of overcrowded alkene.[33]

Disadvantage of this method is that a stoichiometrical amount of a chiral auxiliary has to be used. Furthermore, attempts to couple the analogous five membered cyclic ketone under McMurry conditions, yielded the racemic overcrowded alkene.[34]

In an attempt to improve this method, a route based on a rhodium-catalyzed asymmetric hydrogenation was developed. This work was done in collaboration with Dr. Javier Vicario and Dr. Steve Davey. Substrate **30** could be synthesized via an earlier described method (Scheme 5.5).



Scheme 5.5: Stereoselective synthesis of overcrowded alkene

Hydrogenation of **30** with a mixed ligand system of **L7** and **P2** yielded chiral carboxylic acid **31** in 98% enantioselectivity. The reaction was performed on a multigram scale. A single crystallization from *n*-hexane afforded optically pure **31** in 84% yield. Cyclization via a Friedel-Crafts acylation according to a reported method gave cyclic ketone **32** in 70% yield.[34] No racemization occurred in this step as was determined by chiral HPLC analysis. Initial attempts to couple ketone **32** under standard 'Barton-Kellogg' conditions failed. In all cases, the overcrowded alkene was obtained as a racemic mixture. Applying a combination of elegant work by Furrow *et al.*[35] and the hypervalent iodine mediated 'Barton-Kellogg'

coupling chemistry developed by Feringa *et al.*[36] yielded the overcrowded alkene **33** in 40% yield without lost of enantioselectivity, which was confirmed by HPLC analysis. An advantage of the 'Barton-Kellogg' method compared to the McMurry coupling is the possibility to synthesize unsymmetrical alkenes. In general, the McMurry coupling is used to couple two of the same ketones, to avoid mixtures of products which will be formed when two different ketones are coupled. Because the 'Barton-Kellogg' couples two compounds with two different functionalities, *i.e.* a thioketone with a diazo moiety, it gives the possibility to synthesize unsymmetrical alkenes in good yields without a tedious separation of mixture of products.

5.5 Conclusion

In conclusion, a new catalytic system, based on a mixed ligand approach, has been developed for the rhodium-catalyzed asymmetric hydrogenation of cinnamic acid derivatives with *e.e.'s* up to 99%. The obtained enantioselectivities are comparable to or better than the best enantioselectivities reported for a variety of Rh- and Ru-based catalysts. Easy variation of the chiral and achiral monodentate ligands makes it possible to screen a variety of catalytic systems in a short time. It has been shown further that a catalyst complex based on a hetero-combination of a chiral and an achiral monodentate ligand gives a dramatically higher enantioselectivity than any of the corresponding homo-complexes. Furthermore, ^{31}P-NMR experiments clearly showed the formation of hetero-complexes. In addition, the results obtained from a combination of hydrogenation experiments and ^{31}P-NMR spectroscopy clearly reveals that a fast exchange of ligands takes place until an equilibrium in the ratio of complexes has been reached. The developed method has been applied successfully in the synthesis of chiral overcrowded alkenes.

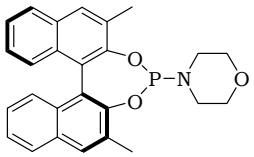
5.6 Experimental section

General Remarks:

For general remarks see chapter 2. Substrates **4**, **5** and **6** were commercially available. Substrates **13**, **14** and **15** were synthesized (see Scheme 5-2). Phosphoramidites **L1** – **L4** were commercially available or made by literature procedures. [37] (*S*)-3,3'-dimethylbinol and phosphoramidite **L5** were generously donated by DSM. Phosphines **P1**-**P11** were purchased from Aldrich or Strem Chemicals.

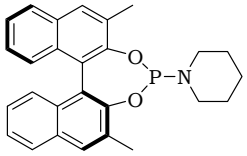
General procedure for the synthesis of ligands **L6**-**L8**:

To a solution of 0.17 ml (1.93 mmol) of PCl_3 and 0.54 ml (3.86 mmol) of Et_3N in 5 ml of toluene at 0°C was added dropwise a solution of 606 mg (1.93 mmol) of (*S*)-3,3'-dimethylbinol in 5 ml of toluene. The reaction mixture was warmed to rt and stirred for 6 h. To the suspension was added 5 ml of ether. The resulting suspension was filtered under N_2 over a path of Celite. To the filtrate was added 0.59 ml (4.24 mmol) of Et_3N. The mixture was cooled to 0°C and 1.93 mmol of the corresponding amine was added dropwise. The mixture was warmed to rt and stirred for 16 h. 5 ml of ether was added to the suspension. The mixture was filtered over celite and the filtrate was concentrated in vacuo. The crude product was purified by a short column chromatography on silica gel (eluens pentane : EtOAc 9:1) to provide the pure products in 60-63% yield.

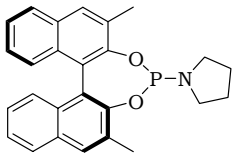


(S)-4-(2,6-Dimethyl-3,5-dioxa-4-phospha-cyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl)-morpholine (**L6**): **^{1}H --NMR** (200 MHz, $CDCl_3$) δ = 7.86–7.79 (m, 4H), 7.42-7.17 (m, 6H), 3.57-3.43 (m, 4H), 3.13-2.95 (m, 4H), 2.63 (s, 3H), 2.58 (s, 3H); **^{31}P-NMR** (81.0 MHz, $CDCl_3$) δ =141.6; **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 148.8 (s), 148.8 (s), 148.4 (s), 131.5 (s), 131.4 (s), 131.2 (s), 130.7 (s), 130.2 (s), 129.7 (s), 129.6 (s), 127.4 (d), 126.8 (d), 126.7 (d), 125.1 (d), 124.7 (d), 124.6 (d), 123.9 (d), 123.8 (d), 122.8 (d), 67.9 (t), 67.8 (t), 44.4 (t), 44.0 (t), 17.7 (q), 17.5 (q) **HRMS** calculated for $C_{26}H_{24}NO_3P$ 429.149 found 429.149; **$[\alpha]_D^{20}$** = -488° (c= 1.08, $CHCl_3$).

(S)-1-(2,6-Dimethyl-3,5-dioxa-4-phospha-cyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl)-piperidine (**L7**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.86–7.77 (m, 4H), 7.42-7.13 (m, 6H), 3.02-2.94 (m, 4H), 2.63 (s, 3H), 2.55 (s, 3H), 1.30-1.59 (m, 6H); **^{31}P-NMR** (81.0 MHz, $CDCl_3$) δ =142.7; **^{13}C-NMR** (52.32 MHz, $CDCl_3$) δ = 149.3 (s), 149.2 (s), 148.8 (s), 131.6 (s), 131.5 (s), 131.1 (s), 130.6 (s),



130.5 (s), 130.4 (s), 130.0 (s), 129.6 (s), 127.4 (d), 126.9 (d), 126.8 (d), 124.9 (d), 124.6 (d), 124.4 (d), 124.0 (d), 123.9 (d), 122.7 (d), 45.2 (t), 44.7 (t), 27.0 (t), 26.9 (t), 24.8 (t), 17.7 (q), 17.5 (q); **HRMS** calculated for $C_{27}H_{26}NO_2P$ 427.170 found 427.171; **[α]$_D^{20}$** = -473° (c= 1.10, $CHCl_3$).



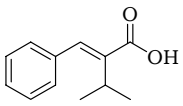
(S)-1-(2,6-Dimethyl-3,5-dioxa-4-phospha-cyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl)-pyrrolidine (**L8**): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.80–7.72 (m, 4H), 7.36-7.10 (m, 6H), 3.14-3.16 (m, 2H), 2.83-2.80 (m, 2H), 2.58 (s, 3H), 2.50 (s, 3H), 1.69-1.63 (m, 4H); **^{31}P-NMR** (161.9 MHz, $CDCl_3$) δ =147.6; **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 149.7 (s), 149.0 (s), 131.6 (s), 131.5 (s), 131.0 (s), 130.6 (s), 130.4 (s), 130.0 (s), 129.5 (s), 129.1 (s), 128.2 (d), 127.4 (d), 127.4 (d), 126.9 (d), 126.8 (d), 124.9 (d), 124.5 (d), 124.4 (d), 123.9 (d), 123.0 (d), 45.65 (t), 45.4 (t), 25.8 (t), 25.8 (t), 17.7 (q), 17.6 (q); **HRMS** calculated for $C_{26}H_{24}NO_2P$ 413.154 found 413.152; **[α]$_D^{20}$** = -445° (c= 1.03, $CHCl_3$).

General procedure for the synthesis of substrates **13**-**15**:[38]

At -20°C, 37.06 ml (92.6 mmol) of *n*-BuLi (2.5M in hexane) was added to a solution of 13.95 ml (99.3 mmol) of diisopropylamine in 60 ml of THF. This mixture was stirred for 30 min at -20°C. Then a solution of 10.97 ml (72.8 mmol) of ethylisovalerate in 40 ml of THF was added. The mixture was stirred for 1 h. Next, a solution of 66.2 mmol of the appropriate benzaldehyde in 40 ml of THF was added at -20°C. The resulting mixture was stirred for 2 h. The reaction was quenched with $NH_4Cl_{(aq)}$ at -20°C. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 ml). The combined organic layers were dried on $MgSO_4$, filtered and concentrated to yield the products in ≥ 90%. The crude products were used without purification in the next step.

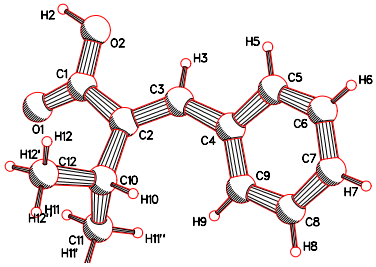
A solution of 78.1 mmol of the crude product and 478 mg (3.90 mmol) of DMAP in 125 ml of THF was cooled to 0°C. 7.4 ml (78.1 mmol) of acetic acid anhydride was added dropwise and the reaction mixture was stirred for 1 hour. A solution of 26.3 g (234.2 mmol) of potassium *t*-butylate in 170 ml of THF was added drop by drop over a period of 30 min at 0°C and the mixture was stirred for 2 h at this temperature. After the addition of 80 ml of water and removal of THF by distillation, 250 ml of ethanol and 35 ml of 2M $KOH_{(aq)}$ was added to the aqueous residue. The mixture was stirred for 20 h under reflux. The reaction mixture was cooled and concentrated. At 0°C, 280 ml of *t*-butyl methyl ether and 120 ml of 2M $HCl_{(aq)}$ were added to the residue. The organic phase was separated and the aqueous phase was extracted again with *t*-butyl methyl ether. The

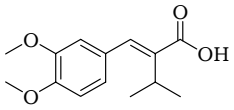
combined organic layers were washed consecutively with water and brine, dried over $MgSO_4$, filtered and concentrated. The product was recrystallized from diisopropyl ether and hexane.



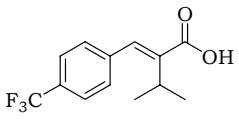
3-Methyl-2-[1-phenyl-meth-(*E*)-ylidene]-butyric acid (**13**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.47-7.26 (m, 5H), 3.28-3.14 (m, 1H), 1.31 (d, *J* = 7.1 Hz, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.7, 140.4, 138.2, 135.7, 128.9, 128.4, 128.3, 27.4, 21.0; **HRMS** calculated for $C_{12}H_{14}O_2$ 190.099 found 190.100. Additional information was obtained from the X-ray structure:

$C_{12}H_{14}O_2$, M_r = 190.24, triclinic, *P*-1, *a* = 6.013(2), *b* = 9.450(3), *c* = 9.751(3) Å, α = 75.168(6)°, β = 76.505(5)°, γ = 78.664(5)°, *V* = 515.3(3) Å^3, *Z* = 2, D_x = 1.226 gcm^{-3}, *F*(000) = 204, *μ* = 0.82 cm^{-1}, λ(MoK$\overline{\alpha}$) = 0.71073 Å, T = 100(1) K, 3296 reflections measured, *GooF* = 1.203, *ωR*(F^2) = 0.1843 for 2222 unique reflections and 183 parameters and *R*(*F*) = 0.0529 for 1738 reflections obeying Fo ≥ 4.0 σ (Fo) criterion of observability. The asymmetric unit consists of one molecule of the title compound.





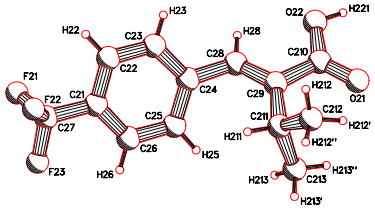
2-[1-(3-Hydroxy-4-methoxy-phenyl)-meth-(*E*)-ylidene]-3-methyl-butyric acid; compound with ethane (**14**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 6.98-6.88 (m, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.33-3.26 (m, 1H), 1.30 (d, *J* = 7.1 Hz, 6H) **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.7, 149.2, 148.6, 140.2, 136.6, 128.2, 122.1, 112.3, 110.9, 55.8, 55.8 27.4, 21.0 **HRMS** calculated for $C_{14}H_{18}O_4$ 250.120 found 250.123.



3-Methyl-2-[1-(4-trifluoromethyl-phenyl)-meth-(*E*)-ylidene]-butyric acid (**15**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 12.09 (bs, 1H), 7.73 (s, 1H), 7.65 (d, 2H, *J* = 8.2), 7.42 (d, *J* = 8.2 Hz, 2H) 3.15-3.02 (m, 1H), 1.29 (d, 6.8 Hz, 6H) **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.0, 140.1, 139.3, 138.6, 129.1, 125.5, 125.4, 27.6, 21.0 **HRMS** calculated for $C_{13}H_{13}O_2F_3$ 258.087

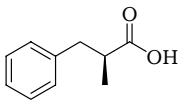
found 258.087. Additional information was obtained from the X-ray structure:

$C_{13}H_{13}F_3O_2$, M_r = 258.24, monoclinic, *C*2/*c*, *a* = 18.249(1), *b* = 13.7838(8), *c* = 20.838(1) Å, β = 110.359(1)°, *V* = 4914.2(5) Å^3, *Z* = 16, D_x = 1.396 gcm^{-3}, *F*(000) = 2144, μ = 1.23 cm^{-1}, λ(MoK$\overline{\alpha}$) = 0.71073 Å, T = 100(1) K, 22892 reflections measured, *GooF* = 1.046, $\omega R(F^2)$ = 0.1223 for 6437 unique reflections and 429 parameters and *R*(*F*) = 0.0450 for 5157 reflections obeying $F_o \geq 4.0\ \sigma(F_o)$ criterion of observability. The asymmetric unit consists of two molecules of the title compound, which forms dimers by hydrogen bonds.

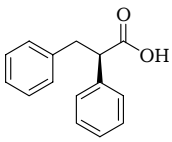


General procedure for hydrogenation reactions:

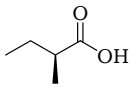
In a glass tube, 4.06 mg (10 µmol) of $Rh(COD)_2BF_4$, 20 µmol of ligand, 1 mmol of the substrate and 4 ml of solvent, was added. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) [39] that was purged 4 times with nitrogen and once with hydrogen and heated if necessary. Then, the autoclave was pressurized with 5 or 25 bar of hydrogen. The reaction mixture was stirred for 16 h. A sample of the resulting mixture was filtered over a silica or Na_2SO_4 plug and subjected to conversion (^{1}H-NMR) and e.e. determination (capillary GC or HPLC). (See Table 5.8) Full conversion was observed in most cases. Absolute configurations were determined by comparison with reference compounds (**24**) or literature data (**12** and **23**)[40], by X-ray analysis (**27**) or assigned by analogy (**25** and **26**).



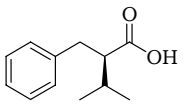
2-Methyl-3-phenyl-propionic acid (**12**) **^{1}H-NMR** (200 MHz, $CDCl_3$)[41] δ = 11.02 (bs, 1H), 7.32-7.25 (m, 2H), 7.23-7.13 (m, 3H), 3.11-3.06 (m, 1H), 2.78-2.75 (m, 1H), 2.70-2.67 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$)[7] δ = 182.8, 139.0, 129.0, 128.4, 126.4, 41.2, 39.2, 16.4; **HRMS** calculated for $C_{10}H_{12}O_2$ 164.084 found 164.087.



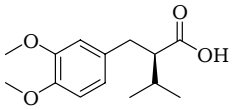
2,3-Diphenyl-propionic acid (**16**): **^{1}H-NMR** (200 MHz, $CDCl_3$)[42] δ = 7.34–7.09 (m, 10H), 3.87 (t, *J* = 7.7 Hz, 1H), 3.42 (dd, *J* = 8.2 Hz, 7.7 Hz, 1H) 3.04 (dd, *J* = 8.2 Hz, 7.7 Hz, 1H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$)[8] δ = 179.3, 138.6, 137.9, 128.9, 128.7, 128.3, 128.1, 127.6, 126.4, 53.4, 39.2; **HRMS**[8] calculated for $C_{10}H_{12}O_2$ 226.099 found 226.101.



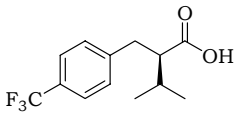
2-Methyl-butyric acid (**17**): **^{1}H-NMR** (200 MHz, $CDCl_3$)[43] δ = 12.12 (bs, 1H), 2.35-2.30 (m, 1H), 1.67-1.60 (m, 1H), 1.46-1.39 (m, 1H), 1.10 (d, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$)[44] δ = 183.7, 40.9, 26.5, 16.3, 11.5; **MS** m/z (%)[5] 102 (M^+, 0.8), 87 (25), 74 (100), 57 (49).



2-Benzyl-3-methyl-butyric acid (**18**): **^{1}H-NMR** (200 MHz, $CDCl_3$)[45] δ = 11.05 (bs, 1H), 7.32-7.14 (m, 5H), 2.89-2.79 (m, 2H), 2.55-2.44 (m, 1H), 2.06-1.89 (m, 1H), 1.35-0.93 (m, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 181.1 (s), 139.6 (s) , 128.8 (d), 128.4 (d), 126.3 (d), 54.8 (d), 35.3 (d), 30.4, 20.3, 20.0; **HRMS** calculated for $C_{12}H_{16}O_2$ 192.115 found 192.114.



2-(3,4-Dimethoxy-benzyl)-3-methyl-butyric acid (**19**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 6.78-6.69 (m, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.83-2.78 (m, 2H), 2.51-2.45 (m, 1H), 2.00-1.90 (m, 1H), 1.18-0.96 (m, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 180.9, 148.7, 147.4, 132.1, 120.6, 112.0, 111.1, 55.8, 55.7, 54.5, 35.0, 30.4, 20.3, 19.9; **HRMS** calculated for $C_{14}H_{20}O_4$ 252.136 found 252.137.



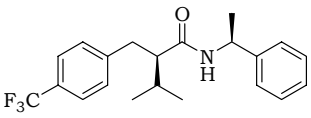
3-Methyl-2-(4-trifluoromethyl-benzyl)-butyric acid (**20**): **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.93-2.84 (m, 2H), 2.55-2.48 (m, 1H), 2.07-1.90 (m, 1H), 1.18-0.95 (m, 6H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 173.4, 136.8, 122.1, 118.3, 118.2, 47.0, 28.0, 23.6, 13.2, 12.9; **HRMS** calculated for $C_{13}H_{15}O_2F_3$ 260.102 found 260.103.

Synthesis of *a*-methylbenzylamine derivative of **20**:

To determine the absolute configuration of **20**, the (*S*)-(-)-*a*-methylbenzylamine derivative of **20** was synthesized.[46] From the resulting product crystals were grown and submitted to X-ray analysis. From the structural data it could be concluded that product **20** has the *R*-configuration.

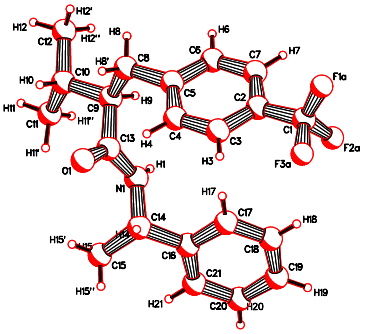
To a cold (0°C) solution of 260 mg (1 mmol) of **20** in 5 ml of CH_2Cl_2 was added a solution of 206 mg (1 mmol) DCC in 10 ml of CH_2Cl_2. The mixture

was stirred for 30 min. To the mixture was added a solution of 0.13 ml (1 mmol) (*S*)-(-)-*α*-methylbenzylamine in 5 ml CH_2Cl_2. The reaction mixture was slowly warmed to rt and stirred overnight. The precipitate was removed by filtration. The filtrate was successively washed with a 2% $HCl_{(aq)}$ solution, a 4% $NaHCO_{3(aq)}$ solution, water, and brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude product was recrystallized from pentane / EtOAc to obtain 30 mg (= 0.083 mmol; 8.3%) of colorless crystals.

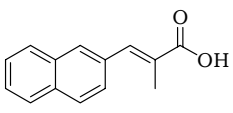


(*R,S*)-3-Methyl-*N*-(1-phenyl-ethyl)-2-(4-trifluoromethyl-benzyl)-butyramide: **^{1}H-NMR** (200 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 8.06 Hz, 2H), 7.17 (m, 5H), 6.82 (m, 2H), 5.27 (bd, *J* = 7.7 Hz, 1H), 5.01 (m, 1H), 2.89 (m, 2H), 1.93 (m, 2H), 1.40 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); **^{13}C-NMR** (50.32 MHz, $CDCl_3$) δ = 177.5, 172.5, 144.5, 142.5, 129.3, 128.4, 127.2, 126.0, 125.2, 58.1, 48.0, 36.4, 31.1, 21.1, 20.8, 20.6; **HRMS** calculated for $C_{21}H_{24}F_3NO$ 363.181 found 363.180; **[α]$_D$** = -21° (c= 0.18, $CHCl_3$).

Absolute configuration assignment was obtained from the X-ray structure:

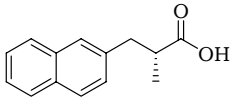


$C_{21}H_{24}F_3NO$, M_r = 363.42, monoclinic, $P2_1$, *a* = 11.180(1), *b* = 4.9299(6), *c* = 17.602(2) Å, β = 96.528(2)°, *V* = 963.87(18) Å^3, *Z* = 2, D_x = 1.252 gcm^{-3}, *F*(000) = 384, *μ* = 0.96 cm^{-1}, λ(MoK$\overline{\alpha}$) = 0.71073 Å, T = 100(1) K, 7298 reflections measured, *GooF* = 1.031, *wR*(*F*^{2}) = 0.1175 for 3682 unique reflections and 359 parameters, 7 restraints and *R*(*F*) = 0.0447 for 3325 reflections obeying $F_o \geq 4.0\ \sigma(F_o)$ criterion of observability.
The asymmetric unit consists of one molecule of the title compound.

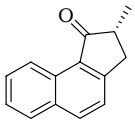


(*E*)-2-Methyl-3-naphthalen-2-yl-acrylic acid (**30**): **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.01 (bs, 1H), 7.85 – 7.93 (m, 4 H), 7.52 – 7.57 (m, 3H), 4.82 (s, 1H), 2.26

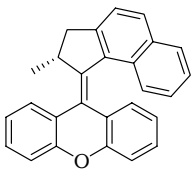
(s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 174.2 (s), 141.2 (d), 133.1 (s), 133.0 (s), 129.8 (d), 128.4 (d), 128.0 (d), 127.7 (s), 127.6 (d), 127.0 (d), 126.9 (d), 126.5 (d), 13.9 (q): **HRMS** calculated for $C_{14}H_{12}O_2$ 212.083 found 212.083.



(*S*)-(+)-2-Methyl-3-naphthalen-2-yl-propionic acid (**31**). An autoclave was loaded with a mixture of 2.0 g (9.43 mmol) of **30**, 78 mg (0.183 mmol) of **L7**, 37.1 mg (0.091 mmol) of $Rh(COD)_2BF_4$, 27.8 mg (0.091 mmol) of P(o-tolyl)$_3$ in 100 ml *i*-PrOH / H_2O (4:1). The autoclave was flushed three times with N_2 and twice with H_2 and subsequently pressurized with 19 bar of H_2. The mixture was stirred for 16 h at 30°C and *i*-PrOH was evaporated under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (100 mL), and the organic solution washed with water (2x50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, pentane:ether = 9:1), affording **31** as a white solid (e.e = 97 %). After crystallization from hexane 1.69 g (84 %) of **31** was obtained as a white solid with e.e. > 99%. **$[\alpha]_D^{20}$** = + 26.2 ° (c = 0.99, CH_2Cl_2). Spectroscopic data were according to the values described in the literature.[34]



(*S*)-(+)-2-Methyl-2,3-dihydro-cyclopenta[a]naphthalen-1-one (**32**). A solution of 1.50 g (7.0 mmol) of **31**, 10 ml of $SOCl_2$ and 1 drop of DMF in 21 ml CH_2Cl_2 was refluxed for 1h. All volatiles were removed under reduced pressure, giving the crude acid chloride, which was dissolved in $ClCH_2CH_2Cl$ and cooled to 0 °C. To the solution was quickly added 2.66 g (20 mmol) of $AlCl_3$ and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched with 50 mL of saturated $NaHCO_{3(aq)}$ and the mixture extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, pentane:ether = 5:1), affording **31** as a white solid (*e.e.* = 97 %). Crystallization from Et_2O afforded 0.97 g (70 %) of **31** with e.e. > 99 % (see Table 5.8). **$[\alpha]_D^{20}$** = + 96.0 ° (c = 1.21, CH_2Cl_2). Spectroscopic data were according to the literature values.[34]



A mixture of 100 mg (0.5 mmol) of **32**, 200 mg (0.75 mmol) 1,2-bis(tert-butyldimethylsilyl)hydrazine and 1 mg (4 mol%) scandium trifluoromethanesulfonate was heated to 100 °C for 4h. Volatile by-products were removed *in vacuo* and the product used without further purification.

To a cooled (-50°C) solution of 162 mg (0.5 mmol) of silylhydrazone in 5 ml of DMF was added 215 mg (0.5 mmol) bis(trifluoroacetoxy)iodobenzene and after 5s, a solution of 135 mg (0.5 mmol) thiocarbonylxanthone in 1.5 ml of DMF. The mixture was allowed to warm slowly to room temperature. The resulting mixture was

partitioned between EtOAc and water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The product was precipitated by addition of cold methanol and collected by filtration (78mg, 40%). Yield reported for 2 steps.

A solution of 70 mg (0.18 mmol) of thiirane and 262 mg (1 mmol) of triphenylphosphine in 5 ml of *m*-xylene was heated to reflux for 16h. After cooling to r.t. 425 mg (3 mmol) of iodomethane was added dropwise and the mixture stirred at r.t. for 1h. The resulting mixture was filtered through a plug of silica eluting with 4: 1 heptane: toluene and the solvent removed *in vacuo* to afford the product as a pale yellow solid (65 mg, 90 %). Spectroscopic data were according to the literature values.[36]

Table 5.8: Ee determination for compounds **12**, **23-27, 31-33**.

Entry	*Compound*	*Method*	R_t *(min)*
1[a]	**12**	A	23.3 (*R*) / 23.5 (*S*)
2	**23**	B	7.5 (*R*) / 8.5 (*S*)
3	**24**	C	9.9 (*S*) / 10.5 (*R*)
4	**25**	D	39.6 (*S*) / 40.9 (*R*)
5	**26**	E	9.7 (*S*) / 12.0 (*R*)
6	**27**	B	15.6 (*R*) / 18.0 (*S*)
7	**31**	F	23.5 (*R*) / 26.3 (*S*)
8	**32**	G	19.3 (*S*) / 22.1 (*R*)
9	**33**	H	3.64 / 3.96

(a) Product was analyzed as its methyl ester; To the crude product in MeOH was added dropwise a 2M solution of trimethylsilyl diazomethane in ether untill the yellow colour persisted

Method A: GC – Chiraldex GTA – 80°C (10 min) -> 3°C/min -> 180°C
Method B: HPLC – Chiralpak AD – 99 : 1 (Heptane : *i*-PrOH)
Method C: GC – Chiraldex BP-M – 80°C isotherm
Method D: GC – Chiraldex BP-M – 135°C isotherm
Method E: HPLC – Chiralcel OD – 95 : 5 (Heptane : *i*-PrOH)
Method F: HPLC – Chiralcel OB – 99 : 1 (Heptane : *i*-PrOH)
Method G: HPLC – Chiralcel OB-H – 99 : 1 (Heptane : *i*-PrOH)
Method H: HPLC – Chiralpak AD – 95 : 5 (Heptane : *i*-PrOH)

^{31}P-NMR experiments:

Spectra were recorded on a Varian Mercuri Plus at a frequency of 162 MHz. Sample preparation: 4.06 mg (0.01 mmol) of $Rh(COD)_2BF_4$ and two or three times 0.01 mmol (2 or 3 equivalents) of ligand were dissolved in 0.8 ml $CDCl_3$. A ^{31}P-NMR was recorded of the resulting yellow solution.

Homo-complexes: **RL_2**: δ 132.7 (d, J_{Rh-L} = 229.5 Hz)
RP_2 : δ 25.9 (d, J_{Rh-P} = 145.5 Hz)

Hetero-complex: **RLP**: δ 135.8 (dd, J_{Rh-L} = 239.2 Hz, J_{L-P} = 35.0 Hz)
δ 30.6 (dd, J_{Rh-P} = 146.3 Hz, J_{L-P} = 35.0 Hz)

5.7 References

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[24] The absolute configuration of **20** was confirmed by X-ray analysis of the corresponding α-methylbenzyl amine derivative. The absolute configuration of **18** and **19** were assigned by analogy (see experimental section).

[25] For clarity reasons the formation of species with only 1 or more than 2 ligands complexed to the rhodium have been left out. Those complexes can be formed, but are in general not observed by ^{31}P-NMR (see §5.3).

[26] The absence of a P-P coupling indicates that the ligands are aligned in an antiparallel way, making the complex C_2-symmetric. This has been observed before in rhodium-phosphoramidite complexes. See ref 22 and PhD thesis of Ate Duursma, University of Groningen, **2004**. Another explanation for the absence of a P-P coupling could be that the ligands are rotating around the rhodium at such a rate that it can not be detected on the time scale of NMR. The two possible

complexes, one were the ligands are aligned parallel and one complex with the ligands aligned antiparallel, will be observed as an 'average complex'. This 'average complex' will have only a rhodium-phosphorus coupling and no phosphorus-phosphorus, since all phosphorus as equal.

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[29] The absolute configuration of **20** was confirmed by X-ray analysis of the corresponding α-methylbenzyl amine derivative. The absolute configuration of **18** and **19** were assigned by analogy (see experimental section).

[30] In the conclusion section of chapter 6 of the PhD thesis of Michel van den Berg (see ref 4a) the conclusion is made: "The possibility of ligand exchange during hydrogenation reaction seems to be small based on the UV and NMR experiments".

[31] MonoPhos™ forms a mixture of complexes on mixing 2 eq. of ligand with 1 eq. of $Rh(COD)_2BF_4$, whereas BINOL-based phosphoramidites only form a single homo-complex (see also reference 4a).

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[46] A sample of **27** with 94% optical purity was used, which was obtained after hydrogenation of **22** under the following conditions: 1 mol% $Rh(COD)_2BF_4$, 2 mol% (*R*)-**L7**, 1 mol% PPh_3, 25 bar H_2, 4 ml *i*-PrOH 20% H_2O, 30°C.

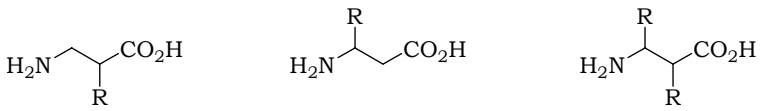
Chapter 6
Rhodium-catalyzed Asymmetric Hydrogenation of β^2-Dehydroamino acids

In this chapter, the rhodium-catalyzed asymmetric hydrogenation of a series of β²-amino acids, with a mixed ligand system consisting of a chiral phosphoramidite and an achiral phosphine, is described. Full conversions and enantioselectivities up to 91% have been achieved.

6.1 Introduction

6.1.1 *β* –Peptides and *β* –amino acids

β-Peptides have been extensively studied in the last ten years.[1] Interesting features of these molecules are that they can fold in a predictable way to form secondary structures in solution. They are resistant to cleavage by peptidases and metabolic transformations and they can mimic α-peptides in protein-protein and peptide–protein interactions. The building blocks for *β*-peptides are *β*-amino acids which can be subdivided in three categories, *i.e.* β^2-, β^3- and $\beta^{2,3}$-amino acids (Figure 6.1).



β^2-amino acid β^3-amino acid $\beta^{2,3}$-amino acid

Figure 6.1: Structures of *β*-amino acids.

6.1.2 Synthesis of β^2-amino acids

A wide variety of methods is known to synthesize enantiomerically pure *β*-amino acids.[2] Most extensively studied is the synthesis of β^3-amino acids although some research has also been focused on β^2-amino acids. Five methods can be distinguished for the synthesis of enantiomerically pure β^2-amino acids:[3]

* Stereoselective alkylation of *β*-homoglycine derivatives

* Addition of chiral enolates to acyliminium salts

* Curtius rearrangement of enantiomerically pure succinates

* Resolution of racemic β^2-amino acids

* Asymmetric transition metal catalyzed reactions

6.1.2.1 Alkylation of β-homoglycine derivatives

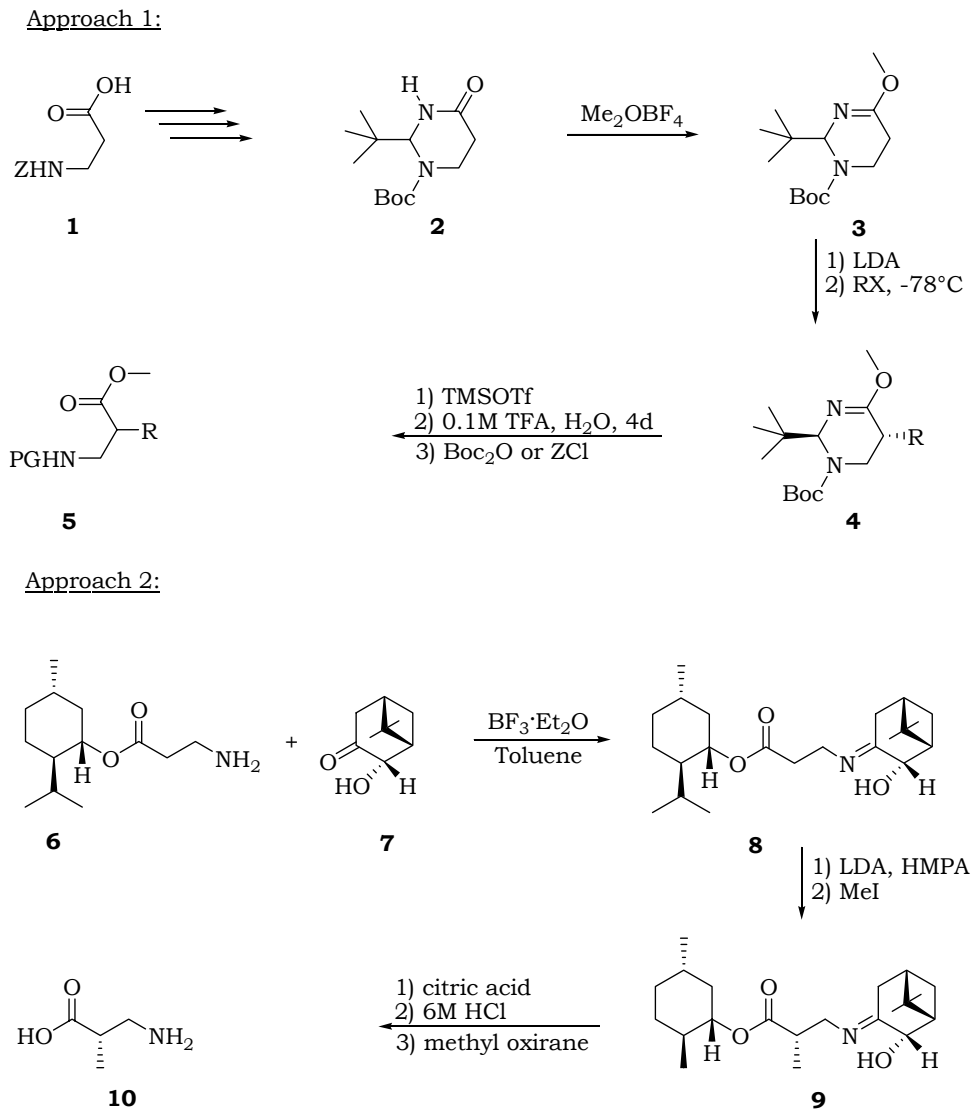
The alkylation of *β*-homoglycine derivatives is the most investigated method for the synthesis of *β²*-amino acids, since *β*-homoglycine is readily available at low cost. In general, *N*-protected *β*-homoglycine is derivatized with a chiral auxiliary and subsequently alkylated. Initial attention has been focused on cyclic derivatives but in the last ten years a number of methods have been reported were acyclic derivatives have been used.[3] Scheme 6.1 shows two representative examples of both approaches. The chiral *β²*-amino acids are obtained after deprotection in good yields and with high selectivity. The stoichiometric amounts of chiral auxiliaries make this method less elegant from an atom economy point of view.

6.1.2.2 Addition of chiral enolates to acyliminium salts

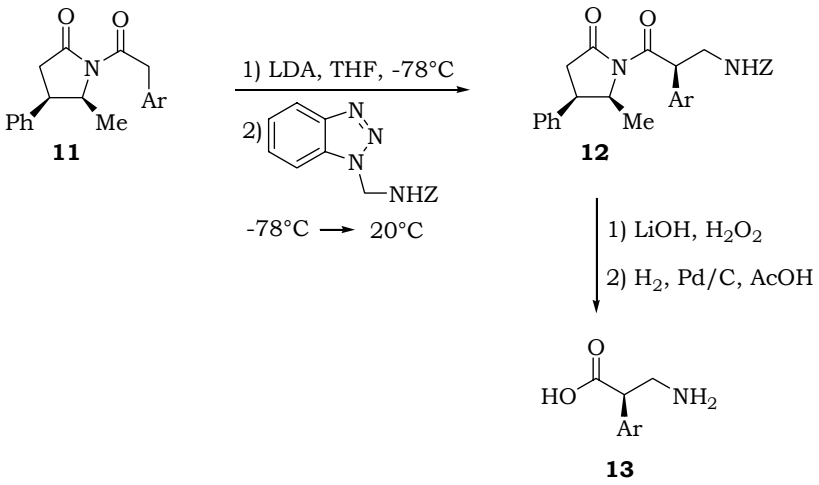
The second method, the addition of chiral enolates to acyliminium salts, is similar to the first method and is also based on enolate chemistry. In a Mannich-type approach, the amine functionality is introduced by alkylation, whereas in the first method this functionality was already present in the enolate. A representative example, developed by Wyatt and co-workers,[4] is depicted in Scheme 6.2. As mentioned before, the use of stoichiometric amounts of chiral auxiliaries makes also this method less elegant.

6.1.2.3 Curtius rearrangement of enantiomerically pure succinates

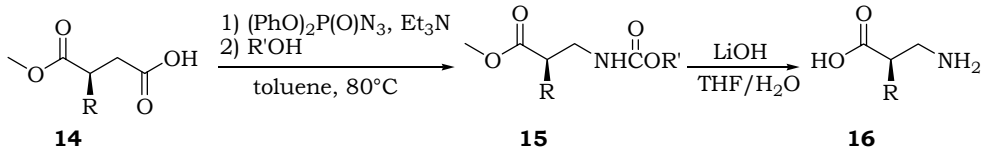
The third route described here is the Curtius rearrangement (see also § 4.2.1.5) of enantiomerically pure and regioselectively protected succinates. This method can lead to either *β²*- or *β³*-amino acids. One of the first examples based on this route has been reported by Monsanto (Scheme 6.3).[5] The preparation of the enantiomerically pure succinates is predominantly done by diastereoselective alkylation of chiral succinyloxazolidinones with alkyl and benzyl halides or by alkylation of acyloxazolidinones with XCH_2CO_2R.[6]



Scheme 6.1: Alkylation of *β*-homoglycine derivatives.[7]



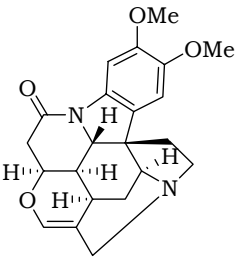
Scheme 6.2: Addition of chiral enolates to acyliminium salts.[4]



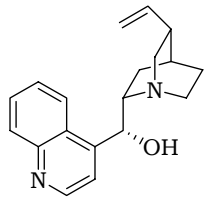
Scheme 6.3: Curtius rearrangement of enantiomerically pure succinates.[5]

6.1.2.4 Resolution of racemic β²-amino acids

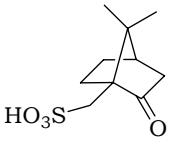
An easy method to obtain enantiomerically pure *β²*-amino acids is by classical resolution. Only a few chiral resolving agents have been reported so far, which have been used in the resolution of *β²*-homoalanine, *β²*-homophenylglycine, *β²*-homoproline and *β²-iso*-proline.[8] The resolving agents are depicted in Figure 6.2.



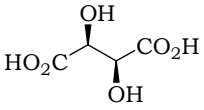
17: Brucine



18: Chinconine



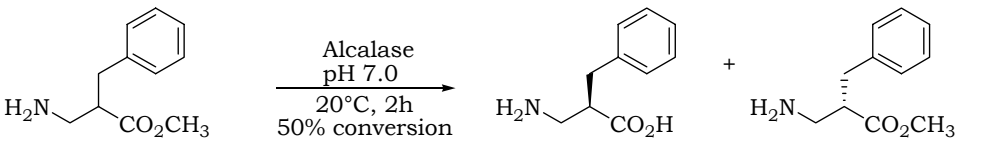
19: Camphor-sulphonic acid



20: Tartaric acid

Figure 6.2: Resolving agents for the classical resolution of *β*[2]-amino acids.[8]

In addition to classical resolution, a number of enzymatic resolutions have been developed.[9] A nice example has recently been reported by DSM.[10] An enzymatic resolution of *β*[2]-phenyl alanine could be performed on a multigram scale (Scheme 6.4).



(*rac*)-**21** methyl ester (*R*)-**21** (*S*)-**21** methyl ester

Scheme 6.4: Resolution of *β*[2]-phenyl alanine by Alcalase 2.5L DX.[10]

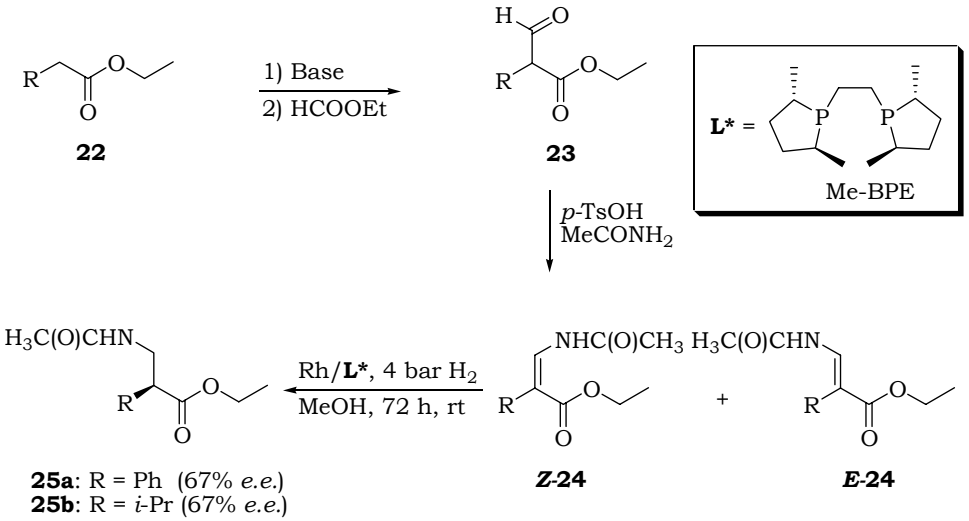
6.1.2.5 Transition metal catalyzed reactions

So far, only a limited number of reports have been published on the synthesis of *β*[2]-amino acids by transition metal catalysis. Among them are Pd-catalyzed allylic substitutions,[11] Rh-catalyzed CH activation,[12] Cu-catalyzed conjugate additions[13] and Rh-catalyzed hydrogenations.[14]

In a series of articles, Robinson and co-workers report on the asymmetric hydrogenation of *β*[2]-amino acids precursors.[14] In an approach were phthalimido nitriles are hydrogenated, which form *β*[2]-amino acids after hydrolysis of the nitrile functionality, modest enantioselectivities (78%) were obtained with Rh-Duphos or Rh-BPE complexes. Another drawback of this method is the synthesis of the substrates. The substrates

are prepared by a Ni-catalyzed addition of the very toxic hydrogen cyanide to alkynes.

A recent article describes the preparation of *β²*-amino acids in three steps (Scheme 6.5). Modest *e.e.'s* (67%) were obtained after rather long reaction times of 72 h.



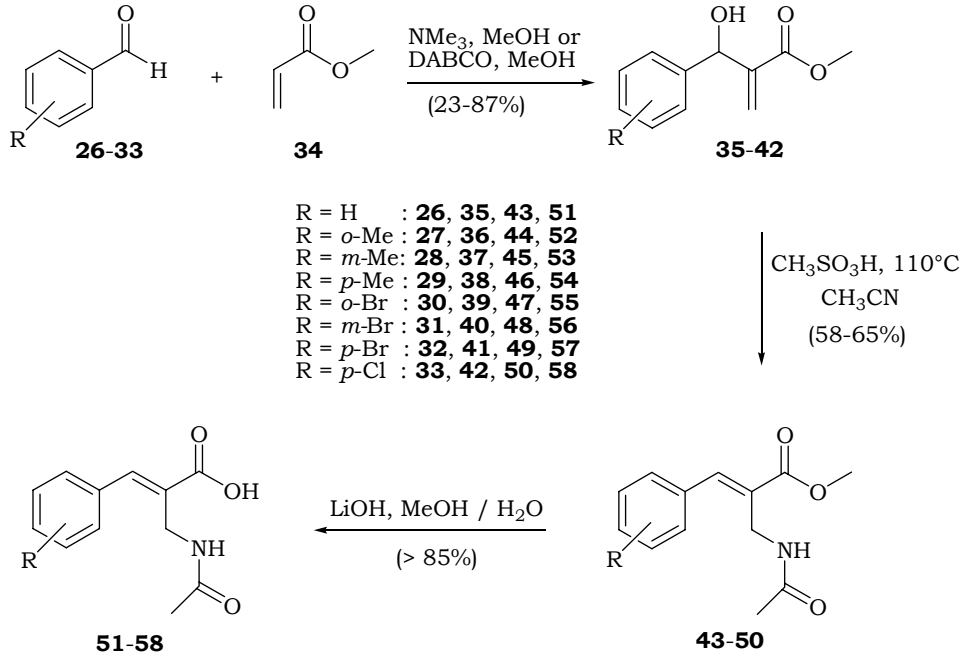
Scheme 6.5: Synthesis of *β²*-amino acids as reported by Robinson *et al.*[14c]

6.1.3 Goal of this research

Basavaiah and Satyanarayana reported the synthesis of *β²*-dehydroamino acid methyl esters in a one-pot synthesis from the corresponding Baylis-Hillman adducts.[16] Although these *β²*-dehydroamino acid methyl esters were undesired products for the authors, we envisioned that these products would be excellent substrates for the rhodium-catalyzed asymmetric hydrogenation. The goal of this research is the asymmetric hydrogenation of these substrates in high enantioselectivities and high yields. This would be a short, elegant and atom economic method for the preparation of *β²*-amino acid derivatives.

6.2 Synthesis of the substrates

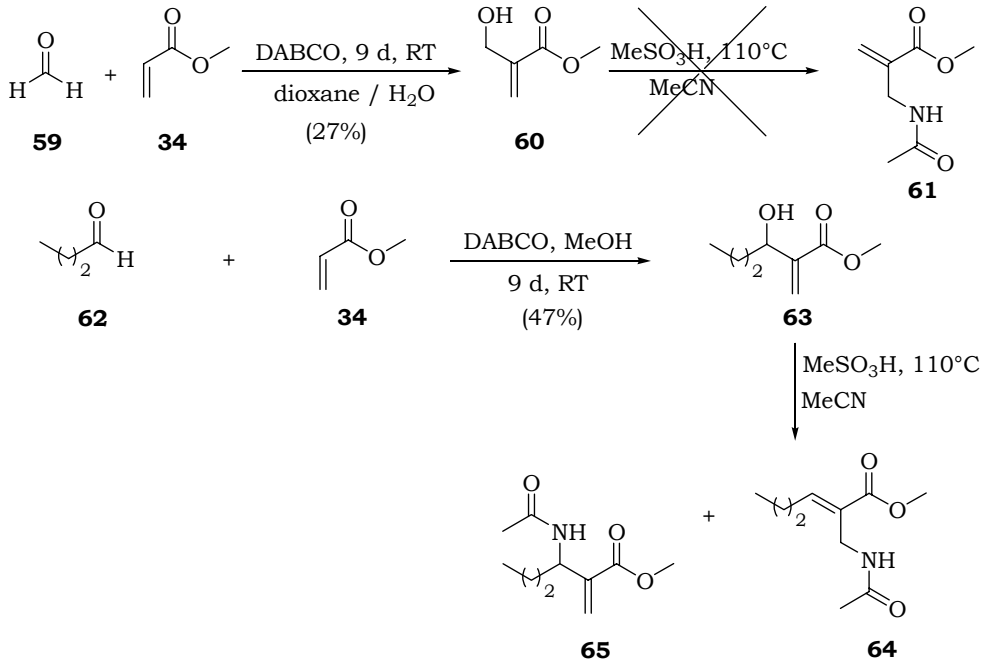
The synthesis of the substrates can be performed, on a multi-gram scale, in three steps starting from the commercially available benzaldehydes and methyl acrylate (**34**) (Scheme 6.6). The initial Baylis-Hillman reaction is well reported[15] and proceeded smoothly with good yields (77-87%) for substrates **35** and **39**-**42**. The yields for the methyl-substituted substrates **36**-**38** were low, due to incomplete conversion, even after 10 d of stirring. This is a general feature for Baylis-Hilman reactions. The introduction of electron donating groups in the starting material decreases the reaction rate, whereas the introduction of electron withdrawing groups increase the reaction rates.



Scheme 6.6: Synthesis of substrates **51-58**.

The second step, which was reported by Basavaiah *et al.*,[16] is a Ritter reaction. This reaction proceeds in good yields with exclusive formation of the *E*-isomer. Dehydroamino acids **51**-**58** could be obtained in high yield after a straightforward hydrolysis of **43**-**50**.

To broaden the scope, attempts were made to synthesize alkyl substituted substrates (Scheme 6.7). The Baylis-Hilman products of methyl acrylate (**34**) with formaldehyde (**59**) and butyraldehyde (**62**) could be obtained in modest yields. Unfortunately, attempts to convert **60** into **61**, using the method as described by Basavaiah *et al.*,[16] failed. After 6 h incomplete conversion was observed. Attempts to separate the starting material from the product by column chromatography were not successful. Increasing the reaction time to 16 h, did not improve the results. A complex mixture of products was obtained.



Scheme 6.7: Attempted synthesis of substrates **61** and **64**.

The Baylis-Hilman product **63** derived from butyraldehyde (**62**) and methyl acrylate (**34**) could be converted by the method of Basavaiah *et al.*[16] Unfortunately, a 1:1 mixture of two regioisomers **64** and **65** was obtained which could not be separated. This can be explained by the formed intermediate. After protonation of the hydroxyl group followed by dehydration, an allyl cation is obtained which is depicted in Figure 6.3. Attack of acetonitrile will mainly take place on resonance structure **B** when R is a phenyl group, since the formed alkene is in conjugation with the

phenyl ring as well as the carbonyl moiety. However, when R is an alkyl group no extra stabilization will take place and acetonitrile will attack in this case on resonance structure **A** as well as on resonance structure **B** which results in an 1:1 mixture of **64** and **65**.

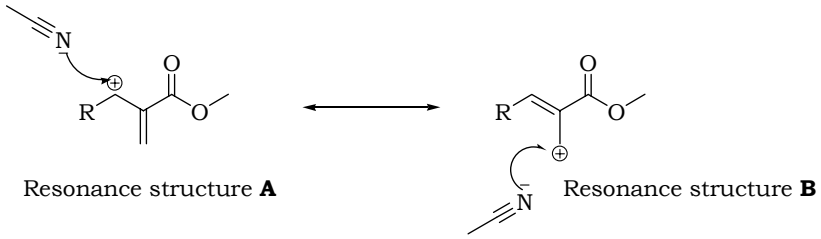


Figure 6.3: Allyl cation formed in the synthesis of the substrates **43**-**50**, **64** and **65**.

6.3 Optimization of the reaction conditions for the enantioselective hydrogenation of 43

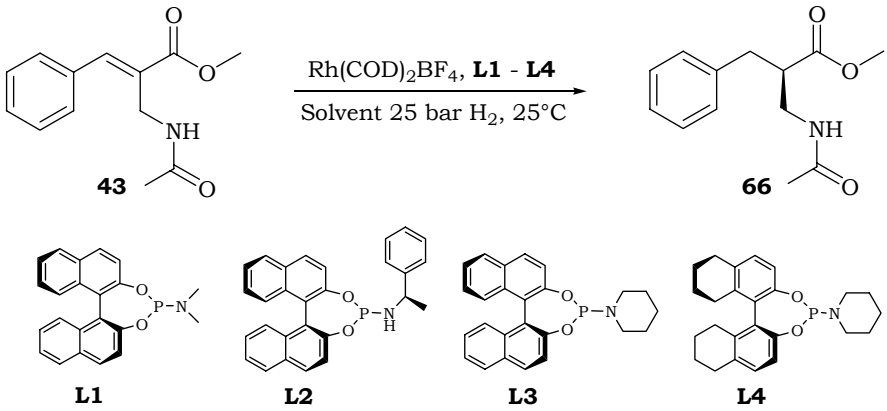
6.3.1 Initial experiments

6.3.1.1 Literature conditions

Initial attempts at the asymmetric hydrogenation of substrate **43**, applying previous developed conditions[17] for the hydrogenation of *α*- and *β*-dehydroamino acids, failed (Table 6.1).

Surprisingly, all reactions performed in CH_2Cl_2 gave no conversion at 25 bar of hydrogen and a temperature of 25°C. The reactions performed in *i*-PrOH gave in some cases low conversions, but the enantioselectivities obtained were rather poor.

Table 6.1: Initial experiments under literature conditions.[a,b,c]



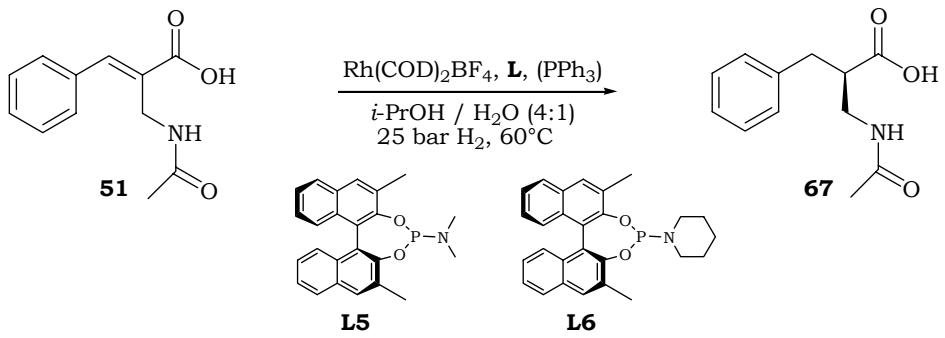
Entry	*Solvent*	*Ligand*	*Conversion*	*E.e.*[d,e]
1	CH_2Cl_2	**L1**	0	-
2	CH_2Cl_2	**L2**	0	-
3	CH_2Cl_2	**L3**	0	-
4	CH_2Cl_2	**L4**	0	-
5	*i*-PrOH	**L1**	20	46
6	*i*-PrOH	**L2**	<10	ND
7	*i*-PrOH	**L3**	0	-
8	*i*-PrOH	**L4**	15	10

(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of solvent with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidite; (b) Reactions were run for 16 h at rt and 25 bar H_2 (c) Conditions are reported in ref. 17a and b; (d) *E.e.'s* were determined by chiral HPLC (for details see experimental section); (e) Absolute configuration of product is not known.

6.3.1.2 The influence of PPh_3

In chapter 5, the rhodium-catalyzed asymmetric hydrogenation of *α,β*-unsaturated carboxylic acids was described.[18] In these cases, addition of an equivalent of an achiral phosphine to the chiral phosphoramidite increased the enantioselectivity and rate of the reaction. Furthermore, the presence of a free carboxylic acid instead of the corresponding methyl ester appeared to be important in the hydrogenation of *α,β*-unsaturated carboxylic acids. Since the structure of **51** is related to the substrates used in the previous chapter, attempts were made to perform the reaction under similar conditions (Table 6.2).

Table 6.2: Influence of PPh_3 in the hydrogenation of **51**.[a,b]



Entry	*Ligand*	*Conversion*	*E.e.*[c,d]
1	**L3**	100	0
2	**L3** + PPh_3	100	66
3	**L5**	100	0
4	**L5** + PPh_3	100	75
5	**L6**	100	0
6	**L6** + PPh_3	100	83

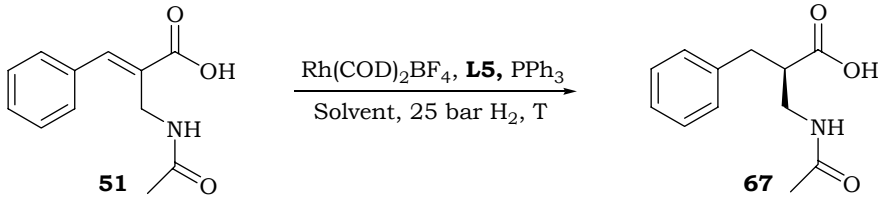
(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of an *i*-PrOH / H_2O (4:1) mixture with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidites and possibly 0.002 mmol of PPh_3; (b) Reactions were run for 16 h at 60°C and 25 bar H_2; (c) *E.e.'s* were determined by chiral HPLC after conversion of product to the corresponding methyl ester (for details see experimental section); (d) Absolute configuration of product is not known.

Raising the temperature to 60°C and adding 20% water as a co-solvent and using the free carboxylic acid led to full conversion, although still a racemic mixture was obtained (compare Table 6.1 entry 7, Table 6.2 entry 1). Addition of an equivalent of triphenylphosphine increased the *e.e.* dramatically. The greatest increase was observed in combination with **L6**. The homo-combination of **L6** showed no selectivity at all, whereas the hetero-combination of **L6** with PPh_3 induced an *e.e.* of 83%. (Entries 5 and 6) As observed before, phosphoramidites substituted with two methyl groups at the 3 and 3' positions of the BINOL moiety, gave higher enantioselectivities than the unsubstituted BINOL based phosphoramidites (entries 2 and 6). Also the introduction of a cyclic piperidine moiety had a beneficial effect on the enantioselectivity (entries 4 and 6).

6.3.1.3 Temperature and solvent optimization

Further optimization of temperature and solvent employing **L5** and PPh_3 as ligands showed that a decrease in temperature, led to a slight increase in *e.e.* (entries 1-7, Table 6.3) An optimal temperature for this system is 40°C, since at lower temperatures no full conversions were obtained.

Table 6.3: Optimization of temperature and solvent.[a,b]



Entry	*Solvent*	*Temperature*	*Conversion*	*E.e.*[c,d]
1	*i*-PrOH / H_2O (4:1)	60	100	75
2	*i*-PrOH / H_2O (4:1)	55	100	77
3	*i*-PrOH / H_2O (4:1)	50	100	78
4	*i*-PrOH / H_2O (4:1)	45	100	78
5	*i*-PrOH / H_2O (4:1)	40	100	78
6	*i*-PrOH / H_2O (4:1)	35	93	76
7	*i*-PrOH / H_2O (4:1)	30	66	80
8	CH_2Cl_2	30	0	-
9	EtOAc	60	0	-
10	MeOH	60	100	77
11	EtOH	60	87	75
12	*i*-PrOH	60	92	69
13	H_2O	60	45	9

(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of solvent with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidites and 0.002 of mmol PPh_3; (b) Reactions were run for 16 h and 25 bar H_2; (c) *E.e.'s* were determined by chiral HPLC after conversion of product to the corresponding methyl ester (for details see experimental section); (d) Absolute configuration of product is not known.

Optimization of the solvent revealed that protic polar solvents were the most suitable for this reaction (entries 8-13). No conversions were obtained in CH_2Cl_2 and EtOAc. This is caused by the poor solubility of the substrates in these solvents. Furthermore, breaking up of the possible internal hydrogen bond in **51**, by protic solvents may also result in an increase of rate and selectivity. The best results were obtained with MeOH:

full conversion and an enantioselectivity of 77%. Other alcohols gave incomplete conversions with slightly lower *e.e.*'s. A solvent mixture of *i*-PrOH and water showed again (see chapter 5) higher selectivity and conversion than the pure solvents. With these results in hand, optimization of the ligands, with respect to the enantioselectivity, was carried out by high-throughput experimentation.

6.3.2 Ligand optimization by high-throughput experimentation

6.3.2.1 High-Throughput Experimentation

One of the most frustrating aspects in homogeneous catalysis is the troublesome rational design of catalysts. Although in some cases well educated guesses can be made regarding structural elements of a good catalyst, optimization of these catalysts is often a matter of trial and error. The synthesis of many (bidentate) ligands is often a time-consuming and tedious work. On the other hand, the synthesis of monodentate phosphoramidites and phosphites is easy. Although the synthesis is short, screening a library of these ligands by hand would take a lot of time. DSM developed an automated method for the solution phase synthesis of monodentate phosphoramidite ligand libraries.[19] Advantage of this method is that a large number of structurally diverse phosphoramidites can be screened in relatively small quantities in a short period of time. The setup of this automated system is depicted in Figure 6.4.

Toluene solutions of a range of phosphorochloridites, amines and triethylamine are dispersed over a 96 wells microplate, consisting of an oleophobic filter. After the dispersion, the microplate is shaken for 2 h on an orbital shaker. The plate is transferred on top of another microplate and vacuum is applied, to remove the formed $Et_3N{\cdot}HCl$ salt by filtration. The toluene solutions with the ligands are dispersed over 96 reaction vials. These are placed in a parallel reactor after addition of solutions of the metal precursor and the substrate. The system is fully automated and all the transferring of solutions is being done by a robot. After completion of the reactions, samples are taken automatically which are subjected to GC and/or HPLC analysis. In earlier reports[19] it has been shown that in general ligands are formed in over 90% purity.

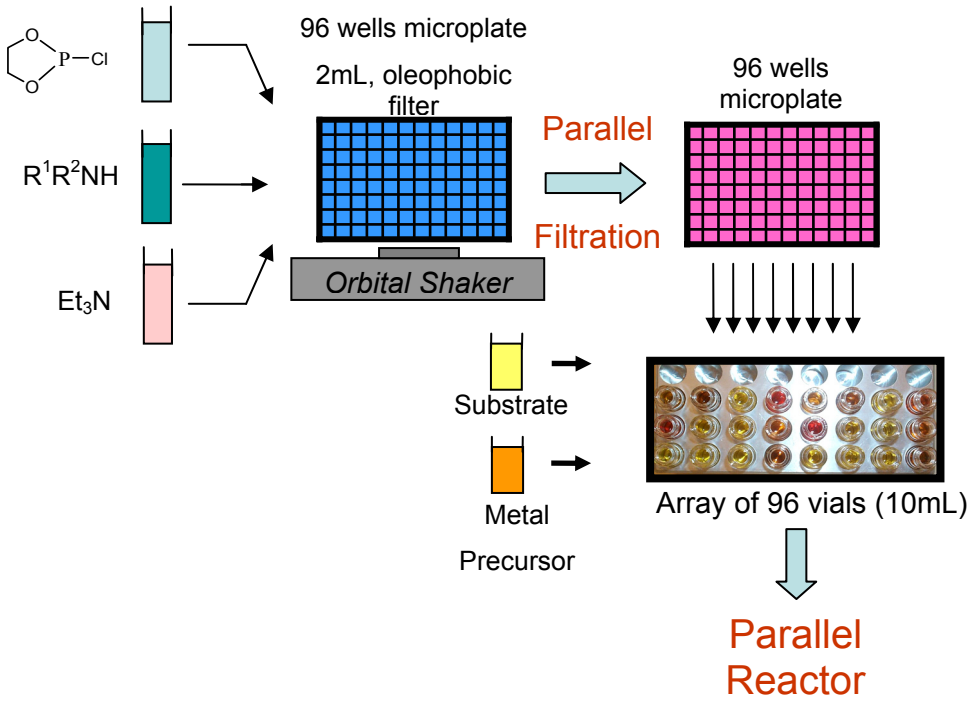
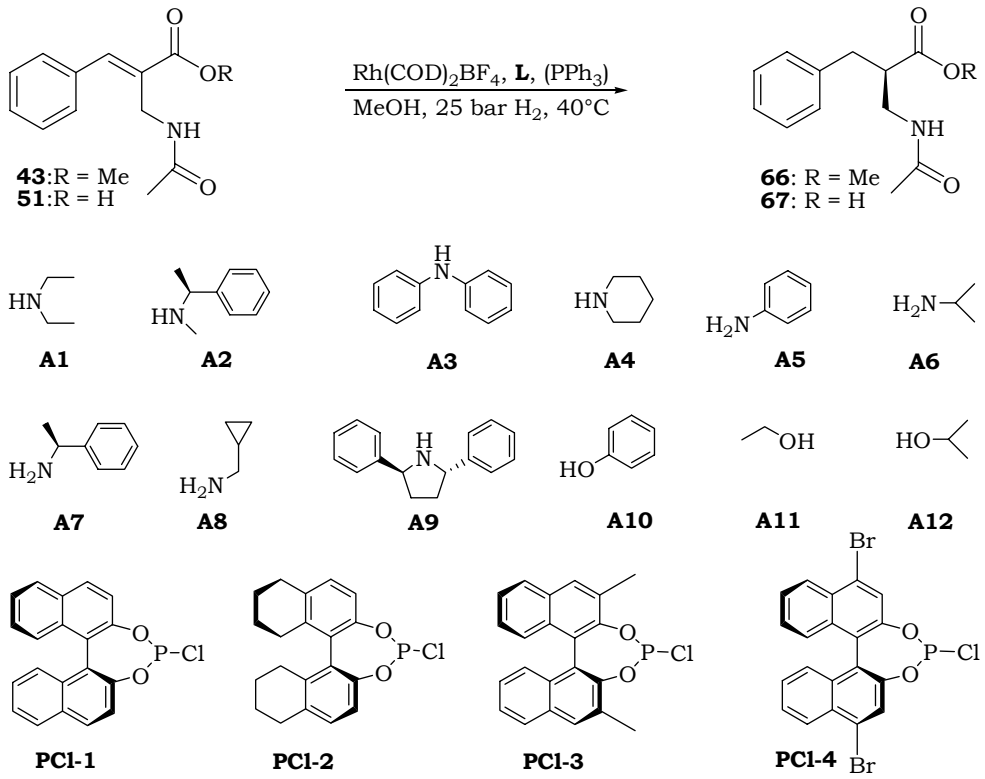


Figure 6.4: High throughput screening of libraries of phosphoramidites.[20]

An initial screening of a library of 48 different phosphoramidites, based on 4 different phosphorochloridites and 12 different amines and alcohols, was done with substrates **43** and **51** at 25 bar of H_2 and 40°C. Screening of substrate **51** was done with an additional equivalent of PPh_3 using the mixed ligand approach as was discussed in chapter 5. The set up of the library is depicted in Scheme 6.8.

The results of the screening on substrate **51** are depicted in Figure 6.5. Ligands based on a 3,3'-dimethyl BINOL (**PCl-3**) induced in most cases full conversion and modest to good *e.e.'s*. On the other hand, ligands based on BINOL (**PCl-1**), 8H BINOL (**PCl-2**) and 4,4'-dibromo BINOL (**PCl-4**) led to relatively low activity with in general poor *e.e.'s*. The enantioselectivities induced by ligands based on primary amines **A5**-**A8** and alcohols **A10**-**A12** were rather poor. The best results were obtained with combinations of **PCl-3** with secondary amines **A1**, **A2** and **A4** (full conversion and 89% *e.e.*).



Scheme 6.8: First screening of a library of phosphoramidites.

Figure 6.6 shows the results of screening the same library of ligands (Figure 6.4) on substrate **43**. As was observed before, ligands based on 3,3'-dimethyl BINOL (**PCl-3**) led to the best conversions. In contrast to what was observed in the hydrogenation of **51**, ligands based on primary amines (**A5**-**A8**) induced higher *e.e.'s* compared to the secondary amines in the hydrogenation of substrate **43**. Similar effects were observed in the rhodium-catalyzed hydrogenation of β^3-amino acids with monodentate phosphoramidites.[17b] In these reactions a ligand based on **PCl-1** and **A7** led to excellent results in the hydrogenation of substrates with a *Z*-geometry at the alkene. Furthermore, monodentate phosphites (**A10**-**A12**) led to rather poor results, with low conversions and enantioselectivities. A combination of **PCl-3** and **A5** gave the best results, with full conversion and 70% *e.e.*

Enantioselectivity

	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
PCl-1												
PCl-2												
PCl-3												
PCl-4												

Conversion

	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
PCl-1												
PCl-2												
PCl-3												
PCl-4												

Figure 6.5: Results of first the library on substrate **51**.

SCALE (%)

0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100

Enantioselectivity

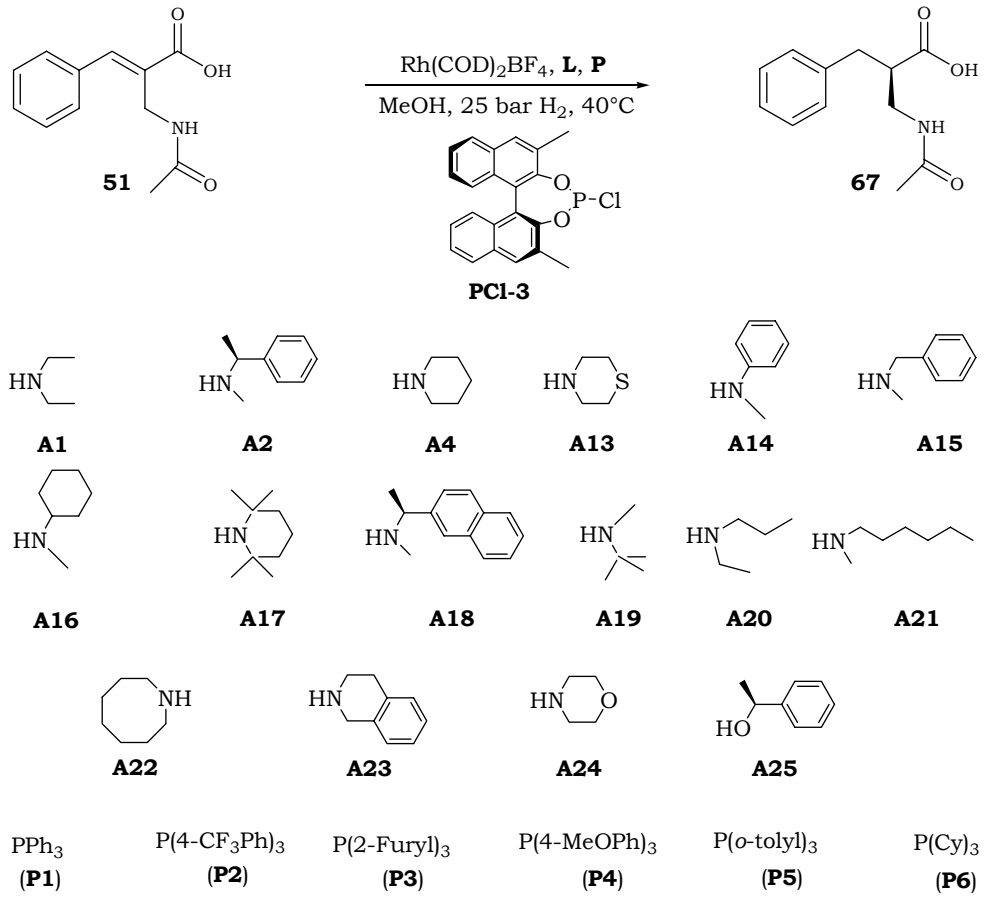
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
PCl-1												
PCl-2												
PCl-3												
PCl-4												

Conversion

	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
PCl-1												
PCl-2												
PCl-3												
PCl-4												

Figure 6.6: of first the library on substrate **43**.

Since the results from the screening of substrate **51** were more promising than those of substrate **43**, the reactions conditions for the asymmetric hydrogenation of **51** were further optimized. A second library with 16 different phosphoramidites based on 3,3'-dimethyl BINOL and 16 different secondary amines was designed. Each phosphoramidite was tested with 6 different phosphines (Scheme 6.9).



Scheme 6.9: Second screening of a library of phosphoramidites on **51**.

The results of the second screening are depicted in Figure 6.7. In general, most of the ligands performed well. Excellent to full conversions were obtained with some exceptions of phosphoramidites based on dialkyl substituted amines and phosphites. For most ligands, enantioselectivities of >80% were obtained with PPh_3 (**P1**) as an achiral co-ligand. Substitution

of the phosphines did not show any improvements. Although modest to good *e.e.'s* were obtained with **P5**, the conversions were in most cases low with this phosphoramidite ligand. A reverse effect was observed with **P6**; good to excellent conversions were obtained, but the enantioselectivities remained low.

Enantioselectivity

	P1	P2	P3	P4	P5	P6
A1						
A2						
A4						
A13						
A14						
A15						
A16						
A17						
A18						
A19						
A20						
A21						
A22						
A23						
A24						
A25						

Conversion

	P1	P2	P3	P4	P5	P6
A1						
A2						
A4						
A13						
A14						
A15						
A16						
A17						
A18						
A19						
A20						
A21						
A22						
A23						
A24						
A25						

SCALE (%)

0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100

Figure 6.7: Results of screening the second library on substrate **51** (Scheme 6.9).

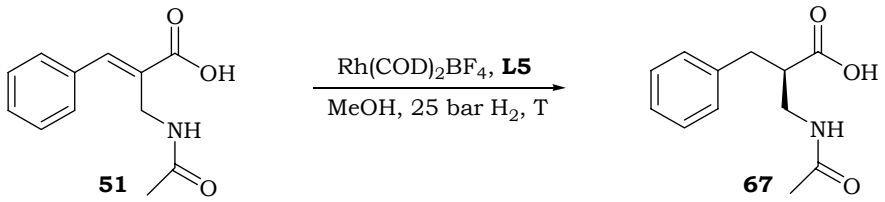
In summary, the results of the screenings showed that **L6** (a combination of **PCl-3** and **A4**) in combination with PPh_3 (**P1**) or P(*o*-tolyl)$_3$ (**P5**) led to the best results in terms of conversion and enantioselectivity (full conversion and 90% *e.e.*).

6.3.3 Further optimization of reaction condition for the hydrogenation of 51

6.3.3.1 Temperature Effect

Another study of the variation in the temperature was performed, since earlier optimization was done for a different solvent. As was observed before, decreasing the temperature increased the enantioselectivity. At 30°C a maximum of 83% *e.e.* was obtained with full conversion. The *e.e.* remained constant when the temperature was decreased even more, but in this case no full conversion was obtained.

Table 6.4: Variation of temperature using methanol as solvent.[a,b]



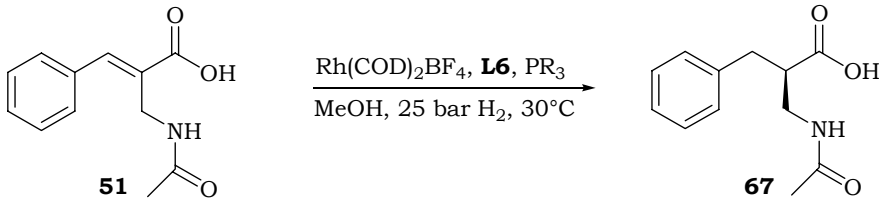
Entry	*Temperature*	*E.e.*[c,d,e]
1	60	77
2	55	80
3	50	80
4	45	82
5	40	82
6	35	82
7	30	83
8	25	83 (96)

(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidite and 0.002 mmol of PPh_3; (b) Reactions were run for 16 h and 25 bar H_2; (c) *E.e.'s* were determined by chiral HPLC after conversion of product to the corresponding methyl ester (for details see experimental section); (d) Conversion is depicted in brackets in case no full conversion is reached; (e) Absolute configuration of product is not known.

6.3.3.2 Phosphine optimization

In chapter 5 it was demonstrated that small alterations in the phosphine structure can have large effects on the selectivity and conversion in the hydrogenation reactions. Table 6.5 represents the results obtained from a screening of structural different phosphines on the hydrogenation of substrate **51** under optimized conditions.[21] Although the variation in enantioselectivity is not as large as for the hydrogenation of *α,β*-unsaturated carboxylic acids, still some small effects can be observed.

Table 6.5: Screening of a variety of phosphines.[a,b]



Entry	*R*	*E.e.*[c,d,e]
1	Ph (**P1**)	89
2	*o*-tolyl (**P5**)	91
3	*m*-tolyl (**P7**)	89
4	*p*-tolyl (**P8**)	85
5	xylyl (**P9**)	85
6	mesityl (**P10**)	33 (53)
7	*m*-ClPh (**P11**)	89
8	*p*-ClPh (**P12**)	88
9	*p*-FPh (**P13**)	87
10	1,2,3,4,5-FPh (**P14**)	0 (12)
11	1-naphthyl (**P15**)	91
12	*p*-MeOPh (**P4**)	66 (88)
13	cyclohexyl (**P6**)	62 (86)
14	*t*-butyl (**P16**)	0 (29)

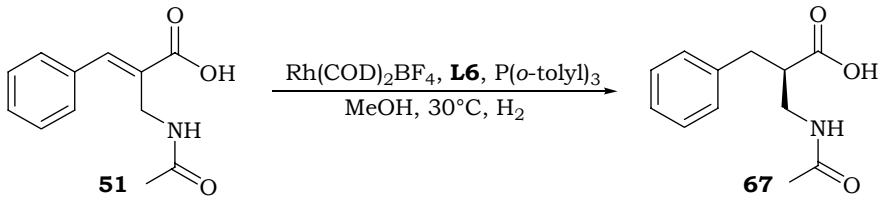
(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidite and 0.002 mmol of PR_3; (b) Reactions were run for 16 h, 25 bar H_2 and 30°C; (c) *E.e.'s* were determined by chiral HPLC after conversion of product to the corresponding methyl ester (for details see experimental section); (d) Conversion is depicted in brackets in case no full conversion is reached; (e) Absolute configuration of product is not known.

Substitution of the phenyl at the ortho position in the triarylphosphine increased the *e.e.* slightly (compare entries 1, 2 and 11). Substitution on other positions did not have any effect. Introduction of electron withdrawing groups did not have any influence on the enantioselectivity (entries 7-9). On the other hand, introduction of an electron donating methoxy group decreased the *e.e.* and the rate of the reaction (entry 12). Sterically crowded phosphines induced low reactivity and low selectivity (entries 6 and 14). Furthermore, alkyl phosphines led to poorer results than aryl phosphines (entries 1, 13 and 14).

6.3.3.3 Pressure optimization

In order to optimize the reaction conditions variation in the pressure was examined. The results are depicted in Table 6.6.

Table 6.6: Screening of hydrogenation at different pressure.[a,b]



51 **67**

Entry	*Pressure*	*E.e.*[c,d,e]
1	25	91
2	20	92
3	15	92
4	10	92 (89)
5	5	92 (64)
6	1	83 (8)

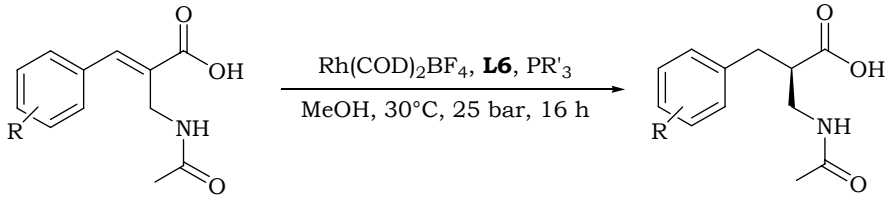
(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of **L6** and 0.002 mmol of P(*o*-tolyl)$_3$; (b) Reactions were run for 16 h at 30°C; (c) *E.e.*'s were determined by chiral HPLC after conversion of product to the corresponding methyl ester (for details see experimental section); (d) Conversion is depicted in brackets in case no full conversion is reached; (e) Absolute configuration of product is not known.

Decreasing the pressure, *i.e.* lowering the hydrogen concentration, had no influence on the enantioselectivity, as was observed in the hydrogenation of *α,β*-unsaturated carboxylic acids. On the other hand, the reaction rate was decreased by lower pressure, as can be seen from the incomplete conversions obtained at pressures lower than 15 bar.

6.3.4 Expanding the range of substrates

The hydrogenations of substrates **52**-**54** and **58** with a variety of phosphines are depicted in Table 6.7.

Table 6.7: Rh-catalyzed hydrogenation of **52-54** and **58**.[a,b]



52-**54**, **58** **68-71**

Entry	*R*	*Product*[c,d,e]	*Phosphines*				
			PPh_3 (**P1**)	P(*o*-tolyl)$_3$ (**P5**)	P(*m*-tolyl)$_3$ (**P7**)	P(*p*-tolyl)$_3$ (**P8**)	P(1-naphthyl)$_3$ (**P15**)
1	*o*-Me (**52**)	**68**	82	90	82	77	- (< 5)
2	*m*-Me (**53**)	**69**	83	86	84	84	91
3	*p*-Me (**54**)	**70**	78	89	81	85	91
4	*p*-Cl (**58**)	**71**	85	80 (65)	79 (90)	78	56 (86)

(a) Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidites and 0.002 mmol of PR_3; (b) Reactions were run for 16 h at 25 bar H_2 and 30°C; (c) *E.e.*'s were determined by chiral HPLC after conversion of the products to their corresponding methyl ester (for details see experimental section); (d) Conversion is depicted in brackets in cases no full conversion is reached; (e) Absolute configuration of products is not known.

The reactions have been performed in MeOH at 25 bar and 30°C. **L6** was used as ligand in combination with phosphines **P1**, **P5**, **P7**, **P8** and **P15**. The highest enantioselectivities for substrates **52**-**54** have been obtained with ortho-substituted phosphines **P5** and **P15** (up to 91% *e.e.*). While for substrates **53** and **54** the best results were obtained with phosphine **P15**, substrate **52** was not converted, probably due to steric hindrance. The enantioselectivities obtained with chloro-substituted substrate **58** was in general lower than for those obtained with the methyl substituted derivatives. In addition to the lower *e.e.*, a drop in reaction rate was observed, which can be seen from the incomplete conversions obtained with phosphines **P5**, **P7** and **P15**. Whereas for **52**-**54** the ortho-substituted phosphines gave the best results, for **58** the less hindered phosphines **P1** gave the highest *e.e.* (85%).

Attempts to hydrogenate the bromo-substituted substrates **55**-**57** did not succeed. In all cases incomplete conversion was obtained. In addition to the desired hydrogenation product, the formation of the dehalogenated products was observed, in combination with some other unidentified side-products.

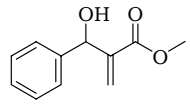
6.4 Conclusion

In this chapter the successful synthesis of β^2-amino acids by asymmetric rhodium-catalyzed hydrogenation, employing a mixture of ligands, has been described. The substrates could be synthesized in a short 4-step procedure with reasonable yields (up to 50% over 3 steps), starting from commercially available aldehydes and methyl acrylate (**34**). Optimization of the catalytic system was done by library screening. Currently the scope of substrates is limited, due to synthetic limitations in the Baylis-Hilman reaction. The presence of electron-donating groups are limiting the synthesis of the Baylis-Hilman adducts. Alkyl substituted substrates could not be synthesized so far due to regioselectivity problems in the Ritter reactions. On the other hand, electron-withdrawing groups in the substrate show worse results in the hydrogenation reactions. The results obtained in the hydrogenations are the best so far reported for this kind of substrates, with a maximum *e.e.* of 91% obtained with **51**, **53** and **54**.[14]

6.5 Experimental section

General Remarks:

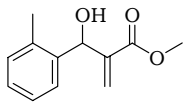
For general information see chapter 2. Phosphoramidites **L1** – **L6** were commercially available or made by literature procedures.[17c] (*S*)-3,3'-dimethylbinol and phosphoramidite **L5** were generously donated by DSM. Phosphines **P1**-**P13** were purchased from Aldrich or Strem Chemicals. The synthesis and screening of the libraries has been done at DSM research in Geleen. The author likes to thank Laurent Lefort and Barbara Procuranti for their contribution to this part.



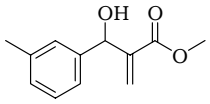
2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (35):[22] To 4.06 ml (40 mmol) of benzaldehyde (**26**) and 10 ml of a 33% (w/v) aqueous solution of Me_3N in 40 ml of MeOH was added 120 mmol of methyl acrylate. The solution was stirred for 48 h and 400 ml of $CHCl_3$ and 100 ml H_2O were added. The layers were separated and the aqueous layer was extracted twice with 100 ml $CHCl_3$. The organic layers were dried on Na_2SO_4, filtered and concentrated. The product was purified by column chromatography. (SiO_2; heptane:EtOAc 5:1) to yield 5.9 g (30.7 mmol; 77%) of a colorless oil. **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.30-7.21 (m, 5H), 6.26 (d, *J* = 6.0 Hz, 1H), 5.83 (s, 1H), 5.48 (d, *J* = 6.0 Hz, 1H), 3.62 (s, 1H), 3.60 (s, 3H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 166.3 (s), 141.9 (s), 141.2 (s), 128.1 (d), 127.4 (d), 126.4 (d), 125.4 (t), 72.4 (d), 51.6 (q); **HRMS** calcd. for $C_{11}H_{11}O_3$ 191.071 found 191.070.

General method for Baylis-Hillman reactions to **36**-**42**.

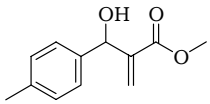
A mixture of 100 mmol of aldehyde, 150 mmol of methyl acrylate and 10 mmol of DABCO in 50 ml of MeOH was stirred at RT until the reaction was completed (monitored by TLC). The mixture was diluted with 150 ml of Et_2O. The organic layer was washed with water (2x 150 ml), brine (150 ml), dried on Na_2SO_4, filtered and concentrated. Products **36**-**42** were purified by column chromatography. (SiO_2; heptane:EtOAc 5:1) Products **36**-**42** were used as obtained.



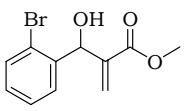
2-(Hydroxy-*o*-tolyl-methyl)-acrylic acid methyl ester (36): 4.65 g (22.6 mmol; 23%) of a colorless oil. **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.73-7.35 (m, 1H), 7.18-7.10 (m, 3H), 6.27 (s, 1H), 5.76 (s, 1H), 5.57 (s, 1H), 3.71 (s, 3H), 2,85 (bs, 1H), 2.28 (s, 3H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 167.1 (s), 141.2 (s), 138.7 (s), 135.6 (s), 130.4 (d), 127.4 (d), 126.2 (d), 126.2 (t), 126.1 (d), 69.2 (d), 52.0 (q), 19.1 (q); **HRMS** calcd for $C_{12}H_{14}O_3$ 206.094 found 206.095.



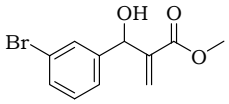
2-(Hydroxy-*m*-tolyl-methyl)-acrylic acid methyl ester (37): 3.17 g (15.4 mmol; 31%) of a colorless oil.[23] **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.21-7.09 (m, 3H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.29 (d, *J* = 1.1 Hz, 1H), 5.81 (d, *J* = 1.1 Hz, 1H), 5.46 (s, 1H), 3.65 (s, 3H), 3.21 (bs, 1H), 2.30 (s, 3H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 166.6 (s), 141.9 (s), 141.1 (s), 137.9 (s), 128.4 (d), 128.2 (d), 127.2 (d), 125.8 (t), 123.6 (d) , 72.9 (d) , 51.8 (q), 21.3 (q); **HRMS** calcd for $C_{12}H_{14}O_3$ 206.094 found 206.095.



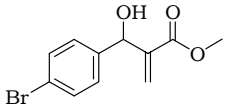
2-(Hydroxy-*p*-tolyl-methyl)-acrylic acid methyl ester (38):[22] 3.64 g (17.7 mmol; 35%) of a colorless oil.[23] **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.28 (d, *J* = 0.9 Hz, 2H), 5.82 (d, *J* = 0.9 Hz, 2H), 5.47 (s, 1H), 3.66 (s, 3H), 3.03 (bs, 1H), 2.29 (s, 3H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 166.7 (s), 142.0 (s), 138.3 (s), 137.4 (s), 129.0 (d), 126.5 (d), 125.7 (t), 72.9 (d), 51.8 (q), 21.0 (q); **HRMS** calcd for $C_{12}H_{14}O_3$ 206.094 found 206.094.



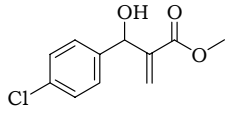
2-[(2-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (39):[22] 23.6 g (87 mmol; 87%) of a colorless oil. **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.44-7.40 (m, 2H), 7.21 (dd, *J* = 7.7 Hz, 7.0 Hz, 1H), 7.04 (dt, *J* = 7.7 Hz, 1.5 Hz, 1H), 6.23 (s, 1H), 5.84 (d, *J* = 4.4 Hz, 1H), 5.51 (s, 1H), 3.80 (d, *J* = 4.4 Hz, 1H), 3.62 (s, 3H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 166.5 (s), 140.6 (s), 139.4 (s), 132.4 (d), 129.0 (d), 128.1 (d), 127.3 (d), 126.7 (t), 122.9 (s), 70.8 (d), 51.8 (q); **HRMS** calcd for $C_{11}H_{11}BrO_3$ 270.979 found 270.981.



2-[(3-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (40):[22] 9.62 g (35.5 mmol; 86%) of a colorless oil.[24] **^{1}H --NMR** (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 1.5, 1H), 7.32 (dd, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.12 (dt, *J* = 7.7 Hz, 1.8 Hz, 1H), 6.27 (s, 1H), 5.80 (s, 1H), 5.40 (d, *J* = 4.4 Hz, 1H), 3.63 (s, 3H), 3.50 (bs, 1H); **^{13}C --NMR** (101.0 MHz, $CDCl_3$) δ = 166.3 (s), 143.6 (s), 141.2 (s), 130.7 (d), 129.8 (d), 129.5 (d), 126.4 (t), 125.1 (d), 122.3 (s), 72.2 (d), 51.9 (q); **HRMS** calcd. for $C_{11}H_{11}BrO_3$ 271.987 found 271.987.



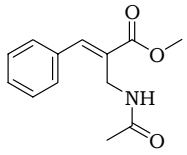
2-[(3-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (41): 23.1 g (85 mmol; 85%) of a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 5.78 (s, 1H), 5.41 (s, 1H), 3.63 (s, 1H), 3.39 (bs, 1H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 166.4 (s), 141.5 (s), 140.3 (s), 131.3 (d), 128.3 (d), 126.1 (t), 121.6 (s), 72.3 (d), 51.9 (q); **HRMS** calcd. for $C_{11}H_{11}BrO_3$ 271.987 found 271.987.



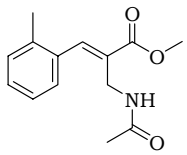
2-[(4-Chloro-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (42):[22] 19.5 g (86 mmol; 86%) of a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.24 (s, 4H), 6.27 (s, 1H), 5.78 (s, 1H), 5.44 (s, 1H), 3.65 (s, 1H), 3.21 (bs, 1H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 166.5 (s), 141.5 (s), 139.7 (s), 133.4 (s), 128.4 (d), 127.9 (d), 126.2 (t), 72.4 (d), 51.9 (q); **HRMS** calcd. for $C_{11}H_{11}ClO_3$ 226.040 found 226.041.

General procedure for the synthesis of **43**-**50**:

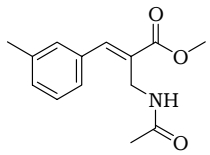
A solution of 80 mmol of Baylis-Hillman adduct in 350 ml of CH_3CN was heated to 60°C. To this mixture was added 215 ml of CH_3SO_3H. The resulting solution was warmed to 110°C and stirred for 6 h. After cooling, the mixture was poured into 150 ml of H_2O. The solution was neutralized with $K_2CO_{3(s)}$ (pH paper). The resulting solution was extracted with Et_2O (2x 400 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. To the remaining yellow solid was added 100 ml of Et_2O. The pure product precipitated as a white solid and was collected (58-65%).



(*E*)-2-(Acetylamino-methyl)-3-phenyl-acrylic acid methyl ester (43):[16] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.42-7.34 (m, 3H), 6.18 (bs, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 1.96 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.6 (s), 168.2 (s), 142.4 (d), 134.0 (s), 129.5 (d), 129.2 (d), 128.6 (d), 127.7 (s), 52.1 (q), 36.7 (t), 23.2 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; **Anal. Calc**. for $C_{13}H_{15}NO_3$: C, 66.92 %; H, 6.49 %; N, 6.01 %, found: C, 66.65 %; H, 6.44 %; N, 5.98 %.

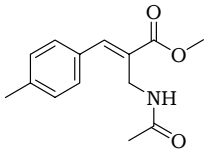


(*E*)-2-(Acetylamino-methyl)-3-*o*-tolyl-acrylic acid methyl ester (44): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H), 7.29-7.14 (m, 4H), 6.05 (bs, 1H), 4.14 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 3H), 2.23 (s, 3H), 1.89 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.3 (s), 168.1 (s), 141.9 (d), 136.7 (s), 133.5 (s), 130.1 (d), 129.1 (d), 128.8 (d), 128.6 (s), 126.0 (d), 52.2 (q), 36.8 (t), 23.3 (q), 19.9 (q); **HRMS** calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.122.

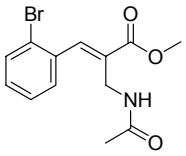


(*E*)-2-(Acetylamino-methyl)-3-*m*-tolyl-acrylic acid methyl ester (45): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.21 (m, 3H), 7.12 (d, *J* = 5.1 Hz, 1H), 6.01 (bs, 1H), 4.28 (d, *J* = 5.5 Hz, 2H), 3.78 (s, 3H), 2.32 (s, 3H), 1.92 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.5 (s), 168.3 (s), 142.7 (d), 138.3 (s), 134.0 (s), 130.3 (d), 130.1 (d), 128.6 (d),

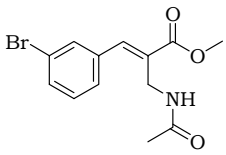
127.5 (s), 126.6 (d), 52.2 (q), 36.8 (t), 23.3 (q), 21.3 (q); **HRMS** calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.122;



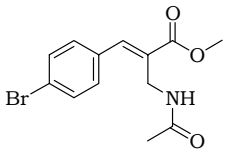
(*E*)-2-(Acetylamino-methyl)-3-*p*-tolyl-acrylic acid methyl ester (46):[16] **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.74 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.27 (bs, 1H), 4.31 (d, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 2.33 (s, 3H), 1.95 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.7 (s), 168.3 (s), 142.6 (d), 139.6 (s), 131.1 (s), 129.6 (d), 129.3 (d), 126.6 (s), 52.1 (q), 36.7 (t), 23.1 (q), 21.3 (q); **HRMS** calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.121.



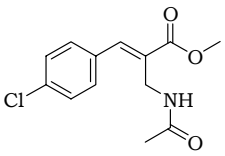
(*E*)-2-(Acetylamino-methyl)-3-(2-bromo-phenyl)-acrylic acid methyl ester (47): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.22 (bs, 1H), 4.16 (d, *J* = 5.5 Hz, 2H), 3.83 (s, 3H), 1.91 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.3 (s), 167.6 (s), 141.2 (d), 134.6 (s), 132.5 (d), 130.6 (d), 130.3 (d), 129.5 (s), 127.5 (d), 123.8 (s), 52.3 (q), 36.7 (t), 23.2 (q); **HRMS** calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.013; **Anal. Calc**. for $C_{13}H_{14}BrNO_3$: C, 50.16 %; H, 4.54 %; N, 4.50 %, found: C, 50.25 %; H, 4.52 %; N, 4.45 %.



(*E*)-2-(Acetylamino-methyl)-3-(3-bromo-phenyl)-acrylic acid methyl ester (48): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.58 (s, 2H); 7.39 (dd, *J* = 7.3 Hz, 7.0 Hz, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.22 (bs, 1H), 4.19 (d, *J* = 5.9 Hz, 2H), 3.74 (s, 3H), 1.87 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.6 (s), 167.8 (s), 140.4 (d), 136.1 (s), 132.3 (d), 132.0 (d), 130.1 (d), 129.2 (s), 127.9 (d), 122.6 (s), 52.2 (q), 36.6 (t), 23.1 (q); **HRMS** calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.014; **Anal. Calc**. for $C_{13}H_{14}BrNO_3$: C, 50.16 %; H, 4.54 %; N, 4.50 %, found: C, 50.30 %; H, 4.53 %; N, 4.48 %.



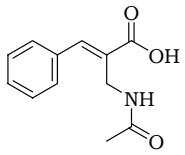
(*E*)-2-(Acetylamino-methyl)-3-(4-bromo-phenyl)-acrylic acid methyl ester (49): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.64 (s, 1H), 7.48 (d, *J* = 8.4, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.30 (bs, 1H), 4.23 (d, *J* = 5.5 Hz, 2H), 3.79 (s, 3H), 1.92 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.6 (s), 167.8 (s), 140.8 (d), 132.8 (s), 131.7 (d), 131.0 (d), 128.4 (s), 123.5 (s), 52.1 (q), 36.5 (t), 23.1 (q); **HRMS** calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.013; **Anal. Calc**. for $C_{13}H_{14}BrNO_3$: C, 50.16 %; H, 4.54 %; N, 4.50 %, found: C, 50.15%; H, 4.51 %; N, 4.48 %.



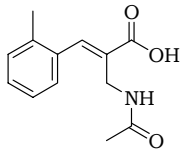
(*E*)-2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-acrylic acid methyl ester (50): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.12 (bs, 1H), 4.31 (d, *J* = 5.9 Hz, 2H), 3.85 (s, 3H), 1.99 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.6 (s), 168.0 (s), 140.9 (d), 135.3 (s), 132.5 (s), 130.9 (d), 128.9 (d), 128.3 (s), 52.2 (q), 36.6 (t), 23.2 (q); **HRMS** calcd. for $C_{13}H_{14}ClNO_3$ 267.066 found 267.066; **Anal. Calc**. for $C_{13}H_{14}ClNO_3$: C, 58.41 %; H, 5.28 %; N, 5.24 %, found: C, 58.45 %; H, 5.22 %; N, 5.21 %.

General procedure for synthesis of **51**-**58**:

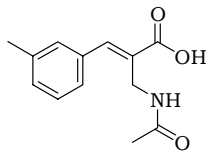
25.8 mmol of ester and 250 mmol of LiOH in 160 ml of a 1:1 mixture of H_2O and MeOH were stirred overnight at RT. The mixture was diluted with 100 ml of H_2O. The aqueous layer was washed with CH_2Cl_2 and then acidified with 2M $HCl_{(aq)}$ until pH = 1. The white precipitate was collected and dried in vacuum oven. The products were obtained as white solids in >85% yield.



(*E*)-2-(Acetylamino-methyl)-3-phenyl-acrylic acid (51): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 12.68 (bs, 1H), 7.98 (bs, 1H), 7.72 (s, 1H), 7.48-7.38 (m, 5H), 4.01 (d, *J* = 4.2 Hz, 2H), 1.82 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.1 (s), 168.3 (s), 141.0 (d), 134.5 (s), 129.5 (d), 129.2 (s), 129.1 (d), 128.6 (d), 36.3 (t), 22.3 (q); **HRMS** calcd. for $C_{12}H_{13}NO_3$ 219.090 found 219.089; **Anal. Calc**. for $C_{12}H_{13}NO_3$: C, 65.74 %; H, 5.98 %; N, 6.39 %, found: C, 65.35 %; H, 5.95 %; N, 6.40 %.

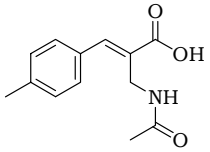


(*E*)-2-(Acetylamino-methyl)-3-*o*-tolyl-acrylic acid (52): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.90 (bs, 1H), 7.76 (s, 1H), 7.29-7.20 (m, 4H), 3.85 (d, *J* = 4.4 Hz, 2H), 2.23 (s, 3H), 1.78 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 168.8 (s), 168.1 (s), 140.1 (d), 136.6 (s), 134.0 (s), 130.1 (s), 129.9 (d), 128.7 (d), 128.5 (d), 125.7 (d), 36.4 (t), 22.4 (q), 19.6 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106;

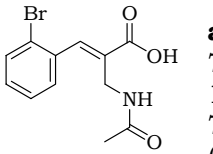


(*E*)-2-(Acetylamino-methyl)-3-*m*-tolyl-acrylic acid (53): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.97 (bs, 1H), 7.68 (s, 1H), 7.33-7.26 (m, 3H), 7.20 (d, *J* = 6.2 Hz, 1H), 4.01 (d, *J* = 4.0 Hz, 2H), 2.30 (s, 3H), 1.83 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.0 (s), 168.5 (s), 141.2 (d), 137.8 (s), 134.4 (s), 130.2 (d), 129.8 (d), 129.0 (s), 128.5

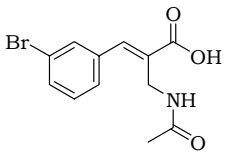
(d), 126.6 (d), 36.3 (t), 22.4 (q), 21.0 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; **Anal. Calc**. for $C_{13}H_{15}NO_3$: C, 66.92 %; H, 6.49 %; N, 6.01 %, found: C, 67.00 %; H, 6.56 %; N, 5.84 %.



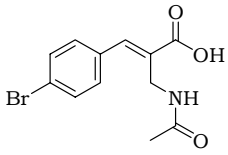
(*E*)-2-(Acetylamino-methyl)-3-*p*-tolyl-acrylic acid (54): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.96 (bs, 1H), 7.68 (s, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.01 (d, *J* = 4.4 Hz, 2H), 2.32 (s, 3H), 1.82 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.1 (s), 168.5 (s), 141.2 (d), 138.9 (s), 131.6 (s), 129.6 (d), 129.3 (d), 128.3 (s), 126.0 (d), 36.4 (t), 22.4 (q), 20.9 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; **Anal. Calc**. for $C_{13}H_{15}NO_3$: C, 66.92 %; H, 6.49 %; N, 6.01 %, found: C, 66.75 %; H, 6.49 %; N, 5.84 %.



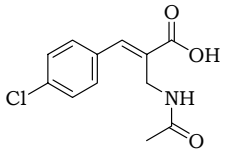
(*E*)-2-(Acetylamino-methyl)-3-(2-bromo-phenyl)-acrylic acid (55): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.95 (bs, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.65 (s, 1H), 7.53 (d, *J* = 5.9 Hz, 1H), 7.43 (dd, *J* = 7.7 Hz, 7.3 Hz, 1H), 7.32 (dd, *J* = 7.7 Hz, 7.3 Hz, 1H), 3.87 (d, *J* = 4.0 Hz, 2H), 1.78 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.0 (s), 167.8 (s), 139.4 (d), 134.7 (s), 132.6 (d), 131.3 (s), 130.7 (d), 130.6 (d), 127.8 (d), 123.6 (s), 36.2 (t), 22.4 (q); **HRMS** calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.999; **Anal. Calc**. for $C_{12}H_{12}BrNO_3$: C, 48.34 %; H, 4.06 %; N, 4.70 %, found: C, 48.40 %; H, 4.03 %; N, 4.67 %.



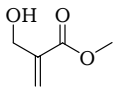
(*E*)-2-(Acetylamino-methyl)-3-(3-bromo-phenyl)-acrylic acid (6): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.99 (bs, 1H), 7.72 (s, 2H); 7,65 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 3.97 (d, *J* = 4.4 Hz, 2H), 1.81 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.1 (s), 168.1 (s), 139.2 (d), 137.0 (s), 131.9 (d), 131.6 (d), 130.9 (s), 130.6 (d), 128.4 (d), 121.9 (s), 36.2 (t), 22.4 (q); **HRMS** calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.998; **Anal. Calc**. for $C_{12}H_{12}BrNO_3$: C, 48.34 %; H, 4.06 %; N, 4.70 %, found: C, 48.35 %; H, 4.00 %; N, 4.65 %.



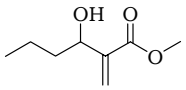
(*E*)-2-(Acetylamino-methyl)-3-(4-bromo-phenyl)-acrylic acid (57): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.00 (bs, 1H), 7.64 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 3.97 (d, *J* = 4.0 Hz, 2H), 1.81 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.2 (s), 168.2 (s), 139.7 (d), 133.8 (s), 131.6 (d) (4x), 130.1 (s), 122.5 (s), 36.2 (t), 22.4 (q); **HRMS** calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.999.



(*E*)-2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-acrylic acid (58): **^{1}H-NMR** (400 MHz, DMSO-d_6) δ = 8.00 (bs, 1H), 7.67 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 3.98 (d, *J* = 4.4 Hz, 2H), 1.81 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 169.1 (s), 168.2 (s), 139.6 (d), 133.7 (s), 133.4 (s), 131.3 (d), 131.0 (s), 128.6 (d), 36.2 (t), 22.4 (q); **HRMS** calcd. for $C_{12}H_{12}ClNO_3$ 253.051 found 253.050; **Anal. Calc**. for $C_{12}H_{12}ClNO_3$: C, 56.82 %; H, 4.77 %; N, 5.52 %, found: C, 56.50 %; H, 4.74 %; N, 5.50 %.



2-Hydroxymethyl-acrylic acid methyl ester (60):[22] A solution of 21.4 g (250 mmol) of 35% aqueous formaldehyde, 67.5 ml (750 mmol) of methyl acrylate, 28 g (250 mmol) of DABCO in 500 ml of a 1:1 mixture of dioxane and H_2O was stirred for 9 d at RT. The mixture was diluted with 150 ml of H_2O. The aqueous layer was extracted with M*t*BE (1x 1 l and 1x 200 ml), washed with brine (2x 400 ml), dried over Na_2SO_4, filtered and concentrated. The product was purified by distillation under reduced pressure. 7.91 g (68.2 mmol; 27%) of a colorless oil was obtained. (46-47°C at 2 mbar). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 6.23 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 3.71 (s, 3H), 3.27 (s, 2H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 167.0 (s), 138.7 (s), 126.2 (t), 54.5 (t), 51.6 (q).



3-Hydroxy-2-methylene-hexanoic acid methyl ester (63):[22] A mixture of 28 g (389 mmol) of butyraldehyde, 54 ml (600 mmol) of methylacrylate, 14.4 g (129 mmol) of DABCO in 100 ml MeOH was stirred for 11 d at RT. The mixture was diluted with 100 ml H_2O. The aqueous layer was extracted Et_2O (2x 100 ml). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The product was purified by distillation under reduced pressure. 28.9 g (183 mmol; 47%) of a colorless oil was obtained. (66-72°C at 1 mbar) **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 6.17 (d, *J* = 2.4 Hz, 1H), 5.76 (d, *J* = 2.4 Hz, 1H), 4.36 (t, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 2.81 (bs, 1H), 1.60-1.49 (m, 2H), 1.47-1.26 (m, 2H), 0.93-0.86 (m, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 166.9 (s), 142.6 (s), 124.7 (t), 71.1 (d), 51.7 (q), 38.3 (t), 18.9 (t), 13.7 (q).

General procedure for the synthesis of solution phase phosphoramidite ligand libraries:

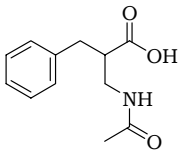
Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in anhydrous toluene (all by weight). For the phosphorochloridites a concentration of 0.150 M was used, for the amines 0.158 M, and for the triethylamine 0.538 M. Using the liquid handling robot in a glovebox 0.333 ml (1.00 eq.) of each of the phosphorochloridites was transferred into one of the 3 corresponding 32 wells of the Whatman PKP filter plate. The triethylamine solution, 0.100 ml (1.00 eq.) was added to each of the 96 wells. Next 0.333 ml (1.05 eq.) of each of the amines was added to one of the 3 corresponding 32 wells of one of the 3 plates. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, *i.e.* the solutions of different phosphoramidites in dry toluene (0.766 ml; 0.065 M) were collected and stored into a 96-well polypropylene microplate.

General procedure for the screening of solution phase phosphoramidite ligand libraries in rhodium-catalyzed hydrogenation of **4** and **5**:

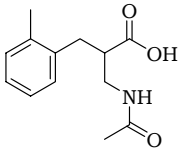
Using the liquid handling robot 0.100 ml (2.0 eq.) of the ligand solutions was transferred from the microplate into 96 vials, equipped with stirring bars. Then 0.1 ml (1.0 eq.) of a 0.0329 M PPh_3 stock solution in DCM,[25] 0.25 ml (0.1 eq.) of a 0.0131 M $Rh(COD)_2BF_4$ stock solution in DCM and 2.25 ml of a 0.073 M (50 eq.) substrate stock solution in MeOH was added. The mixtures were capped under inert atmosphere and transferred to a parallel hydrogenation reactor. The vials were purged with nitrogen and then with hydrogen (25 bar) and heated to 40°C. The reaction mixtures were left stirring for 16 h. Samples of the mixtures were analyzed by chiral HPLC to determine the conversion and the *e.e.*

General procedure for hydrogenation reactions in Endeavor™[26]:

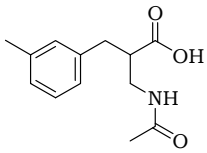
In a glass tube, 0.81 mg (2 µmol) of $Rh(COD)_2BF_4$, 4 µmol of ligand, 0.2 µmol of phosphine, 0.2 mmol of the substrate and 4 ml of solvent, was added. The small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™)[26] that was purged 4 times with nitrogen and once with hydrogen and heated if necessary. Then, the autoclave was pressurized with hydrogen. The reaction was stirred for 16 h. A sample of the resulting mixture was converted into the corresponding methyl ester by 2M solution of trimethylsilyl diazomethane in ether until the yellow color persisted. This sample was filtered over a silica plug and subjected to conversion (^{1}H NMR) and e.e. determination (HPLC).



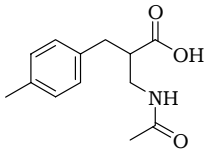
2-(Acetylamino-methyl)-3-phenyl-propionic acid (67): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 9.12 (bs, 1H), 7.25-7.07 (m, 5H), 6.56 (s, 1H), 3.58-3.42 (m, 1H), 3.32-3.22 (m, 1H), 2.98-2.84 (m, 2H), 2.77-2.67 (m, 1H), 1.85 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 177.4 (s), 171.7 (s), 138.0 (s), 128.8 (d), 128.5 (d), 126.6 (d), 46.5 (d), 40.4 (t), 35.7 (t), 22.7 (q); **HRMS** calcd. for $C_{12}H_{15}NO_3$ 221.105 found 221.106.



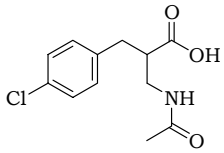
2-(Acetylamino-methyl)-3-*o*-tolyl-propionic acid (68): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = (400 MHz, $CDCl_3$) δ = 9.21 (bs, 1H), 7.15-7.08 (m, 4H), 6.38 (bs, 1H), 3.51-3.38 (m, 2H), 3.06-3.01 (m, 1H), 2.93-2.88 (m, 1H), 2.77-2.72 (m, 1H), 2.31 (s, 3H), 1.92 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 178.1 (s), 171.5 (s), 136.3 (s), 136.2 (s), 130.5 (d), 129.4 (d), 126.8 (d), 126.1 (d), 45.4 (d), 40.7 (t), 33.1 (t), 22.9 (q), 19.4 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.



2-(Acetylamino-methyl)-3-*m*-tolyl-propionic acid (69): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 9.19 (bs, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.03-6.97 (m, 3H), 6.33 (bs, 1H), 3.54-3.49 (m, 1H), 3.36-3.32 (m, 1H), 3.01-2.90 (m, 2H), 2.78-2.73 (m, 1H), 2.30 (s, 3H), 1.92 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 177.9 (s), 171.4 (s), 138.1 (s), 137.9 (s), 129.6 (d), 128.4 (d), 127.4 (d), 125.8 (d), 46.6 (d), 40.5 (t), 35.7 (t), 22.9 (q), 21.3 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.



2-(Acetylamino-methyl)-3-*p*-tolyl-propionic acid (70): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 9.12 (bs, 1H), 7.07 (s, 4H), 6.32 (bs, 1H), 3.53-3.48 (m, 1H), 3.36-3.30 (m, 1H), 3.00-2.89 (m, 2H), 2.79-2.72 (m, 1H), 2.30 (s, 3H), 1.92 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 178.0 (s), 171.4 (s), 136.2 (s), 134.8 (s), 129.2 (d), 128.7 (d), 46.7 (d), 40.4 (t), 35.3 (t), 22.9 (q), 21.0 (q); **HRMS** calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.



2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-propionic acid (71): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 9.22 (bs, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.43 (bs, 1H), 3.52-3.47 (m, 1H), 3.37-3.30 (m, 1H), 2.99-2.88 (m, 2H), 2.78-2.74 (m, 1H), 1.93 (s, 3H); **^{13}C-NMR** (101.0 MHz, $CDCl_3$) δ = 177.4 (s), 171.6 (s), 136.5 (s), 132.5 (s), 130.2 (d), 128.7 (d), 46.6 (d), 40.5 (t), 35.0 (t), 22.9 (q); **HRMS** calcd. for $C_{12}H_{12}ClNO_3$ 255.066 found 255.066.

Table 6.8: *E.e.* determination of **67**-**71**.[a,b]

Entry	Product	Retention Times[c]		
		Enantiomer 1	*Enantiomer 2*	*Starting material*
1	**67**	19.5	21.7	33.0
2	**68**	26.8	31.5	39.9
3	**69**	31.5	35.1	64.1
4	**70**	35.4	40.3	75.5
5	**71**	52.7	59.3	96.6

a) Products were analyzed as their corresponding Me-esters b) All products were analyzed by the same method: RP-HPLC, AD-RH Chiralpak; acetonitrile / NaH_2PO_4 buffer (pH 2.7) 20 : 80 (flow 0.5 ml / min) c) Retention times in min.

Table 6.9: Results of first library on **51** (column 1-4) and **43** (column 5-8).

Amine	*PCl*	*e.e. (%)*	*Conv. (%)*	*Amine*	*PCl*	*e.e. (%)*	*Conv. (%)*
A1	**PCl-1**	67	71	**A1**	**PCl-1**	1	80
A2	**PCl-1**	56	27	**A2**	**PCl-1**	44	6
A3	**PCl-1**	58	16	**A3**	**PCl-1**	1	10
A4	**PCl-1**	65	89	**A4**	**PCl-1**	2	64
A5	**PCl-1**	12	58	**A5**	**PCl-1**	14	34
A6	**PCl-1**	24	100	**A6**	**PCl-1**	38	96
A7	**PCl-1**	34	100	**A7**	**PCl-1**	15	65
A8	**PCl-1**	20	99	**A8**	**PCl-1**	18	82
A9	**PCl-1**	17	81	**A9**	**PCl-1**	9	21
A10	**PCl-1**	2	23	**A10**	**PCl-1**	6	42
A11	**PCl-1**	2	59	**A11**	**PCl-1**	1	53
A12	**PCl-1**	45	100	**A12**	**PCl-1**	6	77
A1	**PCl-2**	49	40	**A1**	**PCl-2**	1	28
A2	**PCl-2**	59	51	**A2**	**PCl-2**	16	13
A3	**PCl-2**	26	19	**A3**	**PCl-2**	14	9
A4	**PCl-2**	50	66	**A4**	**PCl-2**	2	33
A5	**PCl-2**	4	27	**A5**	**PCl-2**	28	71
A6	**PCl-2**	5	79	**A6**	**PCl-2**	55	97
A7	**PCl-2**	13	99	**A7**	**PCl-2**	34	95
A8	**PCl-2**	3	64	**A8**	**PCl-2**	43	87
A9	**PCl-2**	2	70	**A9**	**PCl-2**	21	40
A10	**PCl-2**	2	23	**A10**	**PCl-2**	16	14
A11	**PCl-2**	1	37	**A11**	**PCl-2**	15	26
A12	**PCl-2**	18	60	**A12**	**PCl-2**	21	38
A1	**PCl-3**	89	100	**A1**	**PCl-3**	89	100
A2	**PCl-3**	89	100	**A2**	**PCl-3**	89	100
A3	**PCl-3**	38	19	**A3**	**PCl-3**	38	19
A4	**PCl-3**	89	100	**A4**	**PCl-3**	89	100
A5	**PCl-3**	57	64	**A5**	**PCl-3**	57	64
A6	**PCl-3**	47	100	**A6**	**PCl-3**	47	100
A7	**PCl-3**	53	100	**A7**	**PCl-3**	53	100
A8	**PCl-3**	46	100	**A8**	**PCl-3**	46	100
A9	**PCl-3**	65	100	**A9**	**PCl-3**	65	100
A10	**PCl-3**	29	77	**A10**	**PCl-3**	29	77
A11	**PCl-3**	50	96	**A11**	**PCl-3**	50	96
A12	**PCl-3**	67	100	**A12**	**PCl-3**	67	100
A1	**PCl-4**	24	58	**A1**	**PCl-4**	24	58
A2	**PCl-4**	14	21	**A2**	**PCl-4**	14	21
A3	**PCl-4**	7	15	**A3**	**PCl-4**	7	15
A4	**PCl-4**	31	33	**A4**	**PCl-4**	31	33
A5	**PCl-4**	8	25	**A5**	**PCl-4**	8	25
A6	**PCl-4**	7	80	**A6**	**PCl-4**	7	80
A7	**PCl-4**	11	73	**A7**	**PCl-4**	11	73
A8	**PCl-4**	7	68	**A8**	**PCl-4**	7	68
A9	**PCl-4**	44	96	**A9**	**PCl-4**	44	96
A10	**PCl-4**	5	53	**A10**	**PCl-4**	5	53
A11	**PCl-4**	3	42	**A11**	**PCl-4**	3	42
A12	**PCl-4**	5	57	**A12**	**PCl-4**	5	57

Table 6.10: Results of second library on **51**.

Amine	***P***	*e.e. (%)*	*Conv. (%)*	*Amine*	***P***	*e.e. (%)*	*Conv. (%)*
A1	**P1**	-89	100	**A14**	**P1**	-74	72
A1	**P2**	-76	99	**A14**	**P2**	-63	69
A1	**P3**	-83	99	**A14**	**P3**	-57	47
A1	**P4**	-81	99	**A14**	**P4**	-6	60
A1	**P5**	-76	69	**A14**	**P5**	-39	26
A1	**P6**	-69	99	**A14**	**P6**	15	56
A18	**P1**	-84	99	**A22**	**P1**	-88	100
A18	**P2**	-73	99	**A22**	**P2**	-84	97
A18	**P3**	-79	76	**A22**	**P3**	-86	99
A18	**P4**	-64	34	**A22**	**P4**	-57	27
A18	**P5**	-75	29	**A22**	**P5**	-82	40
A18	**P6**	-49	34	**A22**	**P6**	-68	99
A2	**P1**	-89	100	**A15**	**P1**	-84	99
A2	**P2**	-77	100	**A15**	**P2**	-78	97
A2	**P3**	-77	100	**A15**	**P3**	-71	42
A2	**P4**	-72	99	**A15**	**P4**	-54	15
A2	**P5**	-77	88	**A15**	**P5**	-72	16
A2	**P6**	-66	98	**A15**	**P6**	-63	88
A19	**P1**	-74	72	**A23**	**P1**	-88	76
A19	**P2**	-61	73	**A23**	**P2**	-81	60
A19	**P3**	-65	30	**A23**	**P3**	-77	25
A19	**P4**	-29	77	**A23**	**P4**	-61	21
A19	**P5**	-50	2	**A23**	**P5**	-74	31
A19	**P6**	8	77	**A23**	**P6**	-63	58
A4	**P1**	-90	100	**A16**	**P1**	-89	100
A4	**P2**	-76	100	**A16**	**P2**	-84	96
A4	**P3**	-84	100	**A16**	**P3**	-85	100
A4	**P4**	-89	100	**A16**	**P4**	-84	100
A4	**P5**	-77	75	**A16**	**P5**	-79	94
A4	**P6**	-68	99	**A16**	**P6**	-70	100
A20	**P1**	-86	100	**A24**	**P1**	-87	99
A20	**P2**	-72	100	**A24**	**P2**	-83	97
A20	**P3**	-80	99	**A24**	**P3**	-74	84
A20	**P4**	-77	100	**A24**	**P4**	-63	85
A20	**P5**	-76	57	**A24**	**P5**	-67	25
A20	**P6**	-63	98	**A24**	**P6**	-49	100
A13	**P1**	-90	60	**A17**	**P1**	-63	16
A13	**P2**	-83	68	**A17**	**P2**	-54	22
A13	**P3**	-78	27	**A17**	**P3**	-53	10
A13	**P4**	-75	5	**A17**	**P4**	-12	36
A13	**P5**	-82	6	**A17**	**P5**	-60	3
A13	**P6**	-75	5	**A17**	**P6**	6	19
A21	**P1**	-83	99	**A25**	**P1**	-57	48
A21	**P2**	-76	97	**A25**	**P2**	-40	44
A21	**P3**	-77	90	**A25**	**P3**	-39	29
A21	**P4**	-68	97	**A25**	**P4**	-9	75
A21	**P5**	-72	71	**A25**	**P5**	-8	28
A21	**P6**	-47	95	**A25**	**P6**	11	48

6.6 References

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[21] Optimized conditions are: $Rh(COD)_2BF_4$, **L6** and PR_3 (2:1 ratio of **L6**:PR_3), MeOH, 30°C, 25 bar H_2.

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[23] Reaction was performed on 50 mmol scale.

[24] Reaction was performed on 41 mmol scale.

[25] No PPh_3 was added in the case of substrate **43**.

[26] http://www.argotech.com/products/process_rd/endeavor.html.

Chapter 7
Phenol-based Phosphoramidites

In this chapter the synthesis and application of phenol-based phosphoramidites in rhodium-catalyzed asymmetric hydrogenation reactions are described.

Chapter 7

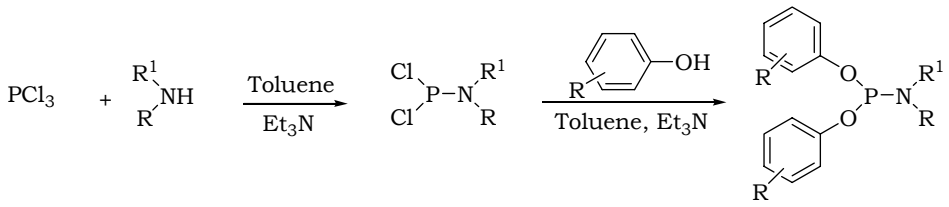
7.1 Phenol-based monodentate phosphoramidites

7.1.1 Introduction

Chapter two describes the successful synthesis and application of catechol-based phosphoramidites. These represent the first examples of monodentate ligands based on an achiral diol backbone. To extend this research, libraries of phenol-based phosphoramidites were screened in the rhodium-catalyzed asymmetric hydrogenation of benchmark substrates. Phenol-based phosphoramidites are known in literature,[1] but to the best of our knowledge chiral equivalents of these ligands have not been synthesized so far. It was reported that these ligands could be isolated in good yields after purification by column chromatography.[1d]

7.1.2 Library setup

The one-step synthesis of libraries of BINOL-based phosphoramidites or phosphites, starts with stock solutions of the corresponding phosphorochloridites and chiral amines (see chapter 6). A two step strategy was chosen for the synthesis of libraries of phenol-based phosphoramidites, starting with stock solutions of PCl_3, phenols and chiral amines (reversed synthetic approach, see also §2.2) (Scheme 7.1).[2]

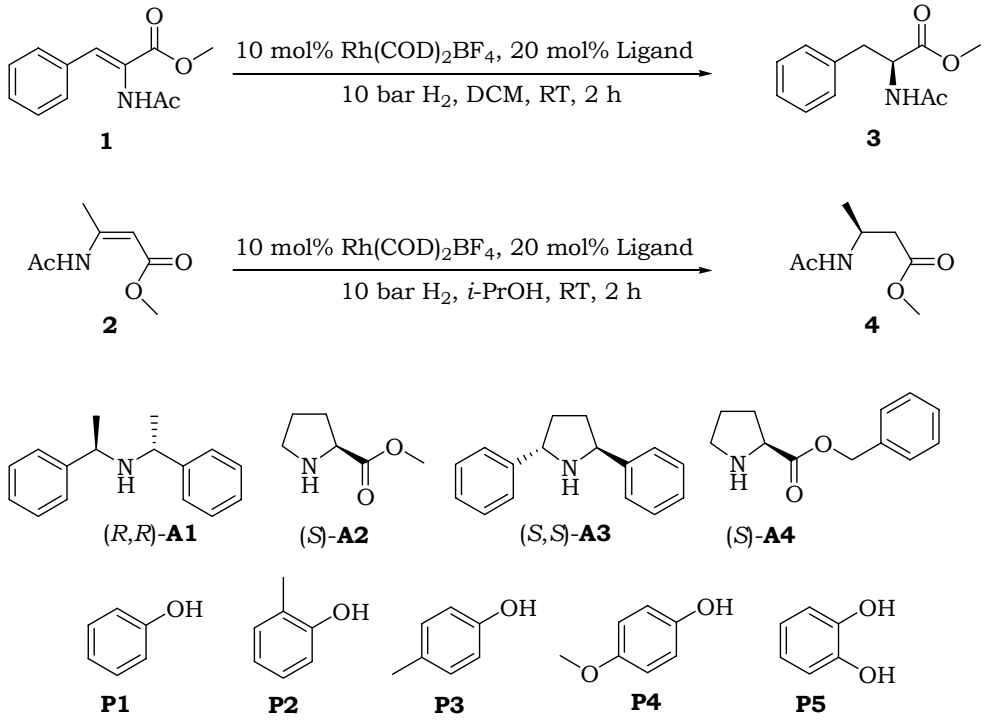


Scheme 7.1: Synthesis of phenol-based phosphoramidites suitable for a library approach.

In the first step, PCl_3 is reacted with one equivalent of an amine. The dichlorophosphino amine subsequently reacts with the corresponding phenol to form a phosphoramidite (for information about conversion and characterization of phosphoramidite libraries, see §7.1.4).

7.1.3 Results

In the first run, a library of 20 phenol-based phosphoramidites was tested in the rhodium-catalyzed asymmetric hydrogenation of *N*-acetyl α-dehydrophenylalanine methyl ester (**1**) and *N*-acetyl β^2-dehydroalanine methyl ester (**2**) (Scheme 7.2). The results of the screening are depicted in Figure 7.1. Four different chiral secondary amines were combined with four different phenols. Catechol was used as a reference to verify the method.



Scheme 7.2: Setup of library 1 for the hydrogenation of **1** and **2**.

Substrate **1**

Conversion

	A1	A2	A3	A4
P1				
P2				
P3				
P4				
P5				

E.e.

	A1	A2	A3	A4
P1				
P2				
P3				
P4				
P5				

Scale (%)

0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100

Substrate **2**

Conversion

	A1	A2	A3	A4
P1				
P2				
P3				
P4				
P5				

E.e.

	A1	A2	A3	A4
P1				
P2				
P3				
P4				
P5				

Figure 7.1: Results of the screening of library 1 on substrate **1** and **2**.

Conversion

	A1	A2	A3	A4
P1				
P6				
P5				

E.e.

	A1	A2	A3	A4
P1				
P6				
P5				

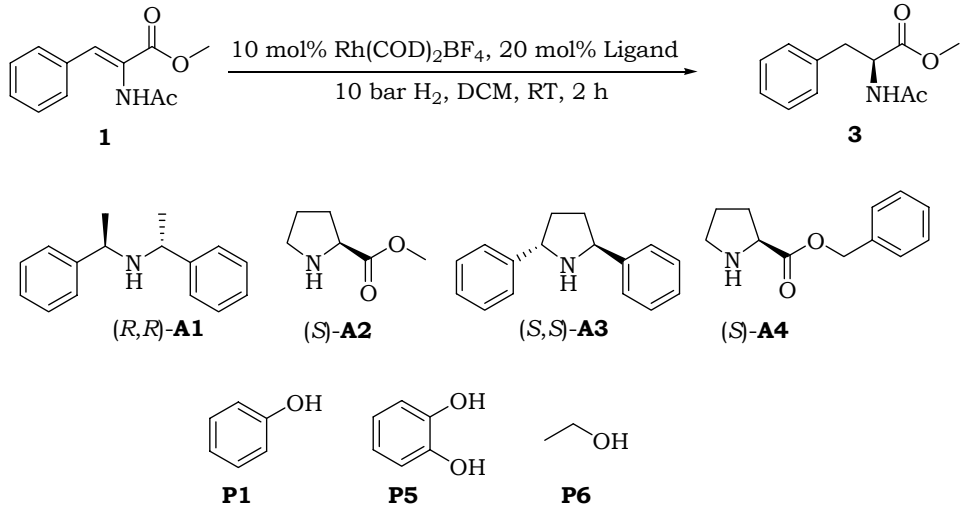
Scale (%)

0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100

Figure 7.2: Results of the screening of library 2 on substrate **1**.

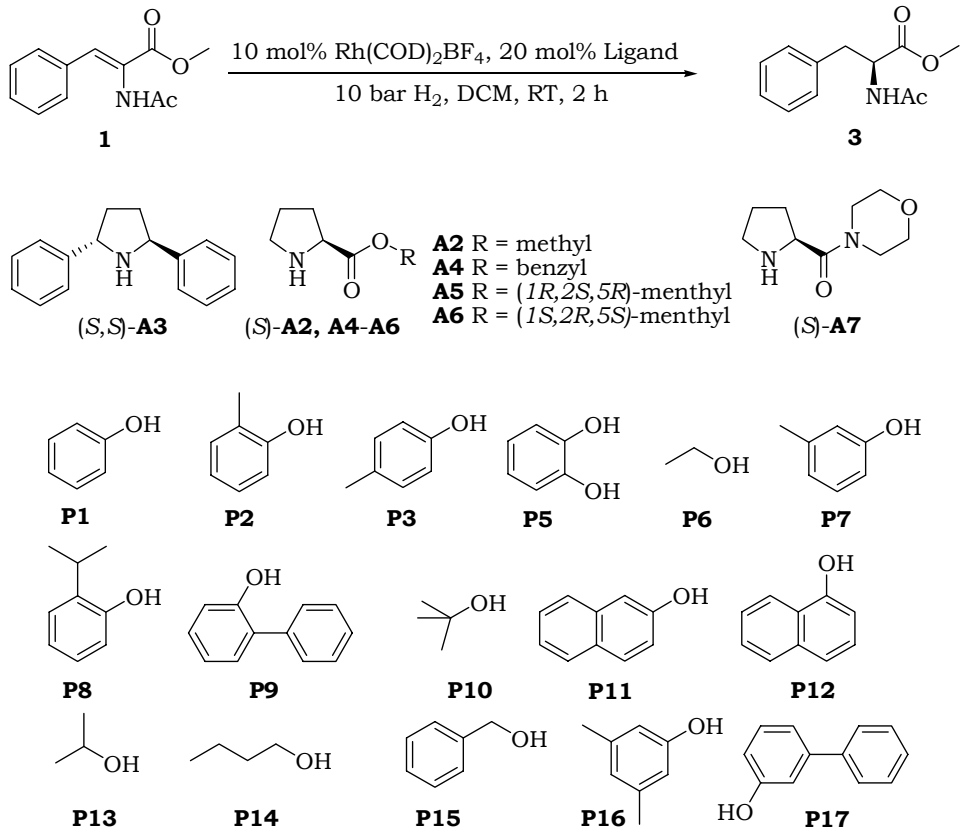
The conversions of substrate **1** show that only catalysts based on ligands with amines **A2** and **A4** gave full conversion, except in the combination with catechol **P5** (Figure 7.1). The enantioselectivities were in all cases low. The only exception was the combination of amine **A3** and catechol (**P5**), with which 86% *e.e.* was obtained. This was a reference reaction since this reaction was performed before with full conversion and 92% *e.e.* (see chapter 2).

Also in the hydrogenation of **2**, catalysts containing phosphoramidites based on amines **A2** and **A4** gave the highest conversions, although these conversions were lower than those obtained with **1** (Figure 7.1). Unfortunately, all the obtained enantioselectivities were low. Again the best result was obtained with a phosphoramidite based on catechol (**P5**) and amine **A3**. The conversion and enantioselectivity are in the same range as those obtained earlier (see chapter 2). It was decided to continue the screening of phenol-based phosphoramidites on substrate **1**. A small second library was designed based on four amines, two phenols and one alcohol (Scheme 7.3). The results of this library are depicted in Figure 7.2.



Scheme 7.3: Setup of library 2 for the hydrogenation of **1**.

Remarkably, in this library all ligands based on phenol (**P1**) gave full conversion, whereas in the first library low conversions were obtained for ligands based on **P1** in combination with **A1** and **A3**. This indicates that the formation of the ligands in the first library did not proceed or that the formation of the catalyst did not take place. Also catalysts bearing ligands based on ethanol (**P6**) gave good to full conversions. In all cases the enantioselectivities were low. The results in this library for the ligands based on catechol (**P5**) should be ignored, since erroneously in the preparation of the ligands, two equivalents of catechol were added instead of one.



Scheme 7.4: Setup of library 3 for the hydrogenation of **1**.

Although the results were disappointing so far, it was decided to design a new library with 96 members (Scheme 7.4). This library was tested again in the hydrogenation of **1**. The library was based on 6 different amines

and16 different phenols or other alcohols. The results of this library are depicted in Figure 7.3. Again catechol (**P5**) based ligands were used as control.

Conversion

	A2	A3	A4	A5	A6	A7
P1						
P2						
P3						
P5						
P6						
P7						
P8						
P9						
P10						
P11						
P12						
P13						
P14						
P15						
P16						
P17						

E.e.

	A2	A3	A4	A5	A6	A7
P1						
P2						
P3						
P5						
P6						
P7						
P8						
P9						
P10						
P11						
P12						
P13						
P14						
P15						
P16						
P17						

0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100

Figure 7.3: Results of the screening of library 3 on substrate **1**.

As can been seen from Figure 7.3, most ligands gave good to full conversions. The only exceptions are ligands based on phenol **P9** and alcohol **P10**. A possible explanation for the low conversions obtained with ligands based on **P9** and **P10** might be the steric hindrance of these compounds. Other ligands based on ortho substituted phenols, *e.g.* **P2**, **P8** and **P12**, also showed lower conversions in most cases. The increase of steric hindrance might be causing difficulties in the formation of the ligands itself or in the formation of the catalytic species.

In all cases the enantioselectivities were low. The best *e.e.* obtained was with the reference ligand based on **P5** and **A3**. One other hit can be observed in

. The phosphoramidite based on **P10** and **A7** induced an *e.e.* of 78%, but with only 2% conversion. This low conversion makes the *e.e.* value arguable. No attempts were made to synthesize this ligand independently, since ^{31}P-NMR spectroscopy revealed that the formation of the ligand in the library did not take place. A typical phosphoramidite absorption in a ^{31}P-NMR spectrum is in the range of 135 to 150 ppm (see §7.1.4). Remarkable then again is the obtained enantioselectivity in the hydrogenation of **1** since no chiral phosphorus ligand was present. This indicates that the free amine compound probably must have act as a ligand. Diamines have been used before successfully as ligands in Rh-catalyzed hydrogenations.[3]

7.1.4 ^{31}P-NMR-analysis of library members

A number of 6 NMR-samples were taken from the library, in order to determine if the formation of the phosphoramidites was successful. The samples were analyzed by ^{31}P-NMR and the results are depicted in Table 7.1.

Table 7.1: ^{31}P-NMR values of some library members.[a,b,c,d]

Entry	*Sample*	*PCl_3*		*$PNCl_2$*		*PO_2N*		*PO_3*		*?*	
		ppm	*%*	*ppm*	*%*	*ppm*	*%*	*ppm*	*%*	*ppm*	*%*
1	**P1 / A4**					137.9	100				
2	**P1 / A5**					137.9	100				
3	**P1 / A7**							128.5	100		
4	**P8 / A3**					141.1	100				
5	**P12 / A3**			162.2	42	141.9	58				
6	**P15 / A4**	224.7	35	150.5	48	142.3	13			67.3	36

(a) All samples were taken in a glovebox under N_2 and diluted with toluene and subsequently subjected to ^{31}P-NMR analysis (b) Ppm values are relative to external H_3PO_4 standard (c) Percentage of total P contents in sample (d) For typical ^{31}P absorptions of compounds, see reference 4.

The samples in entries 1,2 and 4 show only one absorption in the ^{31}P-NMR which can be attributed to the corresponding phosphoramidites, which have at typical absorption between 135 and 150 ppm. Formation of the ligands has been successful in these cases. Remarkably is that even in the case where the more sterically hindered phenol **P8** was used, complete conversion into the phosphoramidite has been observed (entry 4). The ligand based on **P1** and **A7**, bearing an amide functionality, gave only one absorption in the ^{31}P-NMR at 128.5 ppm, which was attributed to triphenylphosphite.[5] In this case, the formation of the initial dichlorophosphino amine had apparently not taken place. The formation of the phosphoramidite based on the sterically demanding **P12** was not complete (entry 5). Two peaks were observed, *i.e.* at 162.2 ppm and 141.9 ppm, attributed to the corresponding dichlorophosphino amine and phosphoramidite. These results suggest that the formation of the initial dichlorophosphino amine was successful. The second step, the reaction of **P12** and the corresponding dichlorophosphino amine, did not go to completion. A mixture of products was obtained in the formation of a phosphoramidite based on benzylalcohol (**P15**) and **A4** (entry 6). Not all the absorptions could be assigned in this mixture. We observed that the reaction of **A4** as well as **P15** with PCl_3 is slow, since traces of unreacted PCl_3 (224.7 ppm) were found.

7.2 Conclusion

The synthesis and screening of libraries of phosphoramidites based on phenol have been described in this chapter. The libraries have been screened in the rhodium-catalyzed hydrogenation of benchmark substrates **1** and **2**. Although in many cases the conversion of the substrates in the hydrogenated products was successful, low enantioselectivities have been obtained. This suggests that the presence of a more rigid diol backbone is necessary for good enantioselectivities.

^{31}P-NMR of representative members of the library revealed that the synthesis of these phosphoramidites was successful in most cases. Only when **A7**, bearing an amide functionality, was used as an amine, no formation of a phosphoramidite was observed. In the case of aliphatic

alcohol **P15** the corresponding phosphoramidite is formed, although in rather low quantities. This proves that the reversed synthetic approach used in this chapter is successful. Although in the rhodium-catalyzed hydrogenation the ligands have not been successful so far, it would be worthwhile to screen these ligands in other types of reactions.

7.3 Experimental section

General remarks:

For general remarks see chapter 2. Amines **A2**-**A7** were made according to literature procedures.[6] **A1** and **P1** - **P17** were commercially available. The synthesis and screening of the libraries of ligands was done at DSM research in Geleen. The author likes to thank Laurent Lefort and Barbara Procuranti for their assistance.

General procedure for the synthesis of solution phase phosphoramidite ligand libraries:

Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in anhydrous toluene (all by weight). For PCl_3 a concentration of 0.269 M was used, for the amines 0.158 M, for the alcohols 0.158 M[7] and for the triethylamine 0.269 M solutions were employed. Using the liquid handling robot 0.100 ml (1.00 eq.) of PCl_3 solution was dispersed over each of the 96 wells of the Whatman PKP filter plate. Then 0.100 ml (1.00 eq.) triethylamine solution and 0.170 ml (1.00 eq.) of the corresponding amines, was added to each of the 96 wells. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. Next, 0.200 ml (2.00 eq.) triethylamine solution and 0.34 ml (2.00 eq.) of the corresponding alcohols, was added to each of the 96 wells. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, *i.e.* the solutions of different phosphoramidites in dry toluene (0.766 ml; 0.030 M) were collected and stored into a 96-well polypropylene microplate.

General procedure for the screening of solution phase phosphoramidite ligand libraries in rhodium-catalyzed hydrogenation of **4** and **5**:

Using the liquid handling robot 0.200 ml (2.0 eq.) of the ligand solutions was transferred from the microplate into 96 vials, equipped with stirring bars. Then 0.25 ml (0.1 eq.) of a 0.013 M $Rh(COD)_2BF_4$ stock solution in DCM and 2.00 ml of a 0.015 M (10 eq.) substrate stock solution in DCM[8] was added. The mixtures were capped under inert atmosphere and transferred to a parallel hydrogenation reactor. The vials were purged with nitrogen and then with hydrogen (10 bar). After purging, the vials were pressurized with 10 bar of H_2. The reaction mixtures were left stirring for 2 h. Samples of the mixtures were analyzed by chiral GC to determine the conversion and the *e.e.* (see chapter 2 for details on chromatographic separation).

Table 7.2: Results of library 1 on substrate **1** and **2**.

Conversion substrate **1**

	A1	**A2**	**A3**	**A4**
P1	9	100	21	100
P2	0	100	24	100
P3	15	100	4	100
P4	9	100	10	100
P5	6	5	100	31

E.e. product **3**

	A1	**A2**	**A3**	**A4**
P1	-4	-1	19	-6
P2	0	0	-9	-1
P3	-2	-1	14	-7
P4	-4	-1	34	-15
P5	-7	-2	86	-11

Conversion substrate **2**

	A1	**A2**	**A3**	**A4**
P1	0	31	3	15
P2	0	52	8	57
P3	0	39	10	49
P4	0	25	5	44
P5	2	0	51	1

E.e. product **4**

	A1	**A2**	**A3**	**A4**
P1	0	-1.3	48	0
P2	0	-12	-6	-15
P3	0	22.1	31	25
P4	0	3.43	31	1
P5	-2	0	66	8

Table 7.3: Results of library 2 on substrate **1**.

Conversion substrate **1**

	A1	**A2**	**A3**	**A4**
P1	97	100	97	100
P6	52	100	61	100
P5	3	1	1	0

E.e. product **3**

	A1	**A2**	**A3**	**A4**
P1	-3	-1	0	-18
P6	-20	0	13	-7
P5	-1	0	0	0

Table 7.4: Results of library 3 on substrate **1**.

Conversion substrate **1**

	A2	**A3**	**A4**	**A5**	**A6**	**A7**
P1	16	100	100	61	54	100
P2	23	96	77	25	61	100
P3	16	100	100	98	100	100
P5	99	13	11	70	72	18
P6	35	99	98	44	100	68
P7	13	100	100	86	98	100
P8	35	71	38	41	100	100
P9	10	3	3	4	3	16
P10	0	11	11	17	18	2
P11	11	92	99	79	94	96
P12	13	24	20	11	23	100
P13	81	100	100	63	100	96
P14	92	99	100	100	100	100
P15	99	100	100	98	100	100
P16	11	100	100	100	100	100
P17	8	91	91	76	93	96

E.e. product **3**

	A2	**A3**	**A4**	**A5**	**A6**	**A7**
P1	18	-9	-12	-8	-10	**-3**
P2	-5	-2	-2	-2	-4	-4
P3	24	-16	-10	-15	-9	-5
P5	83	-4	-7	-9	-3	-4
P6	-3	-7	-14	-12	-12	-3
P7	21	-10	-13	-11	-8	-4
P8	-12	-5	-3	-3	-2	-5
P9	8	-10	0	-11	-9	-7
P10	20	-2	-2	-2	8	78
P11	15	-9	-12	-9	-5	-4
P12	-21	3	-3	1	0	-1
P13	9	-6	-12	-9	-6	-5
P14	9	-6	-14	-14	-6	-4
P15	9	-6	-5	-6	-5	-6
P16	20	-6	-9	-7	-5	-5
P17	11	-11	-9	-13	-12	-6

7.4 References

[1] For examples see: (a) Dąbkowski, W.; Tworowska, I.; Michalski, J.; Cramer, F. *Tetrahedron Lett.* **2000**, *41*, 7535-7539 (b) Heliński, J.; Dąbkowski, W.; Michalski, J. *Tetrahedron Lett.* **1993**, *34*, 6451-6454 (c) Eritja, R.; Smirnov, V.; Caruthers, M. H. *Tetrahedron* ***1990***, 46, 721-730 (d) Van Rooy, A.; Burgers, D.; Kamer, P. C.; Van Leeuwen, P. W. N. M. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 492-498.

[2] Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586-2590.

[3] Jones, M. D.; Raja, R.; Thomas, J. M.; Johnson, B. F. G.; Lewis, D. W.; Rouznard, J.; Harris, K. D. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4326-4331.

[4] "*Spektroskopische Methoden in der Organischen Chemie*", 5th ed., Hesse, M.; Meier, H.; Zeeh, B. Thieme Verlag, Stuttgart, **1995**.

[5] A reported literature value for triphenylphosphite is 127.9 ppm, see: Van Manen, H-J.; Nakashima, K.; Shinkai, S.; Kooijman, H.; Spek, A. L.; Van Veggel, F. C. M. J.; Reinhoudt, D. N. *Eur. J. Inorg. Chem.* **2000**, 2533-2540.

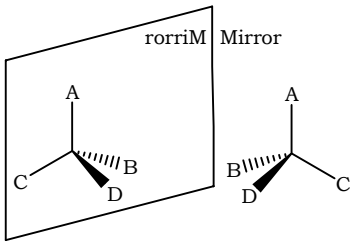
[6] (a) Xin, Z-q.; Da, C-s.; Dong, S-l.; Liu, D-x.; Wei, J.; Wang, R. *Tetrahedron: Asymm.* **2002**, *13*, 1937-1940 (b) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymm.* **2000**, *11*, 2455.

[7] For the stock solution of catechol (**P5**) a concentration of 0.079 M was used.

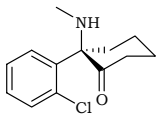
[8] For substrate **2** a stock solution in *i*-PrOH was used.

Summary

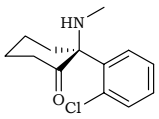
New approaches in asymmetric rhodium-catalyzed hydrogenations with monodentate phosphoramidites



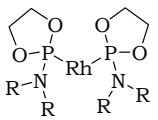
Molecules are spatial structures of atoms. Carbon (C) is one of the most abundant atoms in nature. Carbon can have maximum 4 substituents, which form together with the central carbon atom a tetrahedral structure. Two different kinds of structures are possible when those 4 substituents are different. These two structures are mirror images and can not be superimposed. These molecules are chiral or asymmetric. The two mirror images are also named enantiomers. Enantiomers have the same physical properties, *i.e.* boiling point, melting point, molecular weight etc. The only aspect in which they differ is the optical activity and the interaction with other chiral molecules, like for example enzymes in the human body. The importance of chiral molecules can be illustrated by the following example; Ketamine can be used as an anesthesia if the correct enantiomer is administered. The other enantiomer on the other hand has hallucinating properties. This example shows that it can be important to use only one enantiomer of biological active compounds.



(*R*)-Ketamine
Hallucinating



(*S*)-Ketamine
Anasthesia



One way to obtain enantiomers is via chemical reactions. Normally a chemical reaction is not selective and both enantiomers will be formed in equal amounts. A possibility to influence a reaction, so that only one of the two enantiomers will be formed, is by adding a small amount of a chiral catalyst. The catalysts that are described in this thesis consist of a metal (rhodium) which is surrounded by two chiral ligands, *i.e. chiral monodentate phosphoramidites*. These monodentate phosphoramidites are organic molecules and possess a phosphorus atom which is bound to two oxygens and one nitrogen atom. They are called monodentate, because these ligands coordinate with only one position to the metal. Monodentate ligands change the properties of the metal and cause that the metal stays in solution. The use of a chiral catalyst in a chemical reaction does not automatically mean that only one enantiomer is formed. The selectivity of the catalyst is expressed in *e.e.* (*enantiomerically excess*) of the chiral product formed. An *e.e.* of 0% corresponds to

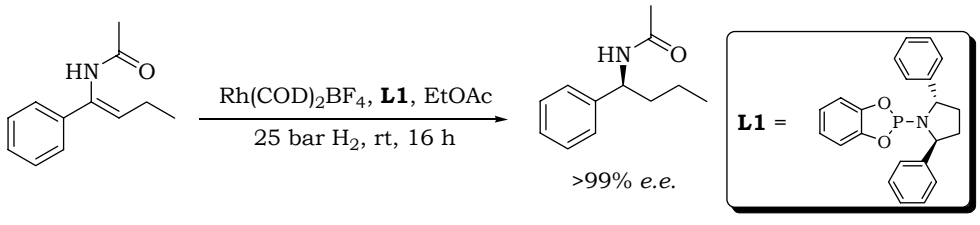
an equal amount of both enantiomers, whereas 100% corresponds with the presence of solely one of the two enantiomers.

This thesis describes the development of new homogeneous* catalysts, which are used to make chiral compounds by asymmetric hydrogenation reactions.

Contents of this thesis

An introduction into chirality is given in chapter 1, followed by a short historical overview of the developments in the field of homogeneous asymmetric hydrogenation as well as the current state of the art using monodentate ligands. Until a few years ago, mainly bidentate† ligands were used in asymmetric catalysis. The structure of monodentate ligands can be modified easily due to the straightforward synthesis of monodentate ligands. On the other hand, modification of the structure of bidentate ligands is often more difficult. This, in combination with the fact that monodentate ligands give equally good results in several asymmetric catalysis reactions, made that there has been a rapid increase in the development of monodentate ligands in the last six years. The chapter finishes with an overview of the application of monodentate ligands in asymmetric catalysis in the last two years. The overview has been limited to the use of monodentate phosphoramidites due to the extended number of publications in this field.

Most successful chiral monodentate ligands used in asymmetric hydrogenation reactions are based on a chiral backbone. The first examples of the synthesis and use of monodentate phosphoramidites possessing an achiral catechol-backbone are presented in chapter 2. These catechol-based ligands gave excellent results in de asymmetric hydrogenation of a number of substrates. An example is given in Scheme 1.

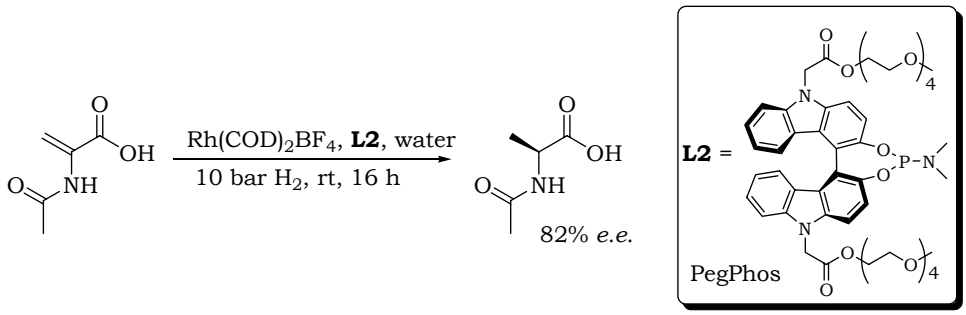


Scheme 1: Asymmetric hydrogenation with phosphoramidites **L1**.

* Homogeneous means that the catalyst is soluble in the reaction medium

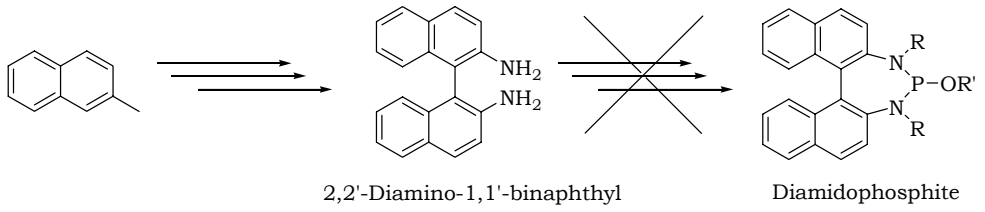
† Bidentate means that the ligand is coordinated to the metal with two positions

In general organic solvents are used for hydrogenation reactions. On the other hand, water is rarely used, because a lot of catalysts are not soluble or stable in water. The synthesis and application of the first water-soluble monodentate phosphoramidite, PegPhos (**L2**), are described in chapter 3 (Scheme 2).



Scheme 2: Asymmetric hydrogenation with PegPhos (**L2**) in water.

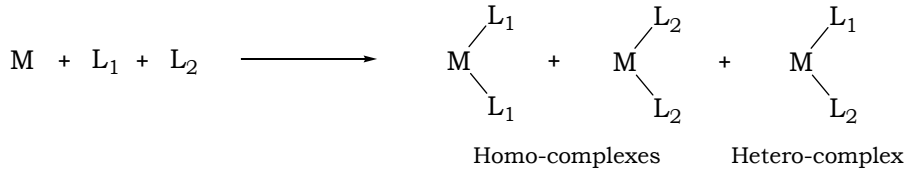
Monodentate phosphoramidites are excellent ligands for rhodium-catalyzed hydrogenations. On the other hand monodentate diamidophosphites are hardly reported as ligands for asymmetric catalysis. Chapter 4 describes the synthesis of 2,2'-diamino-1,1'-binaphthyl and the attempts to make monodentate diamidophosphites out of it (Scheme 3).



Scheme 3: Attempted synthesis of diamidophosphites.

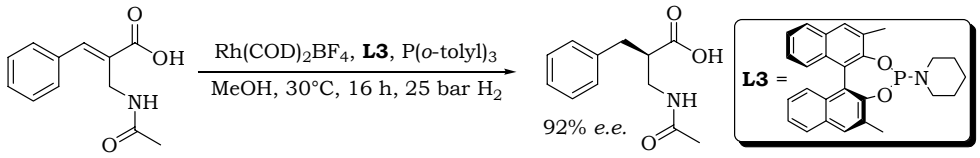
The asymmetric hydrogenation of unsaturated carboxylic acids, using a mixed monodentate ligand approach, is described in chapter 5. In this approach a combination of two different monodentate ligands are used instead of two identical ligands. A mixture of three catalysts is obtained when employing a combination of two different monodentate ligands, *i.e.* 2 homo-complexes (2 identical ligands coordinated to the metal) and 1 hetero-complex (2 different ligands coordinated to the metal) (Scheme 4). This will lead to better results if the hetero-complex shows a higher rate and is more selective in the catalytic reaction then the corresponding homo-complexes.

The combination of ligands, described in this chapter, consist of a chiral phosphoramidite and an *achiral* phosphine. Remarkably, the addition of an achiral ligand to a chiral phosphoramidite increases the reaction rate as well the enantioselectivity of the product. The formation of the hetero-complexes has been proven by ^{31}P-NMR spectroscopy. The products obtained are interesting intermediates among other things for molecular motors or medicines.



Scheme 4: The mixed monodentate ligand approach.

The mixed monodentate ligand approach, using a combination of a chiral phosphoramidite and an achiral phosphine, has also been employed in the asymmetric hydrogenation of *β*^{2}-dehydroamino acids (Scheme 5). Ligand optimization has been done by an automatic system. Enantioselectivities up to 92% have been achieved. The results are described in chapter 6.

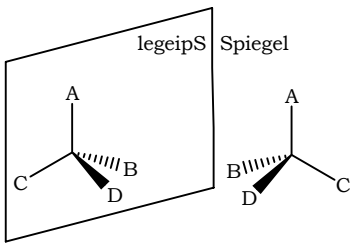


Scheme 5: Asymmetric hydrogenation of *β*^{2}-dehydroamino acids.

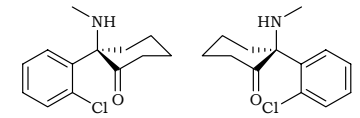
The synthesis and screening of phenol-based phosphoramidites, using an automatic system, are described in chapter 7. In most cases good reactivities were obtained, although the enantioselectivities were poor in all cases. The formation of the ligands has been studied by ^{31}P-NMR spectroscopy, which showed that in most cases the phenol-based phosphoramidites were formed.

Samenvatting

Nieuwe ontwikkelingen in asymmetrische rhodium-gekatalyseerde hydrogeneringen met monodentaat liganden

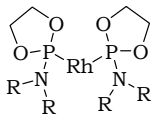


Moleculen zijn ruimtelijke structuren opgebouwd uit atomen. Koolstof (C) is een van de meest voorkomende atomen in de natuur. Koolstof kan worden omringd door maximaal vier substituenten, die samen met het koolstofatoom een tetraedrische structuur vormen. Wanneer deze vier substituenten verschillend zijn, zijn er twee verschillende structuren mogelijk (zie inzet). Deze twee mogelijke structuren zijn spiegelbeelden van elkaar en kunnen niet over elkaar gelegd worden. Deze moleculen worden asymmetrisch of chiraal genoemd. De twee spiegelbeelden worden ook wel enantiomeren genoemd. Enantiomeren hebben dezelfde fysische eigenschappen zoals kookpunt, smeltpunt, molecuul gewicht enz. Het enige waarin ze verschillen is de optische activiteit en de interactie met andere chirale verbindingen, zoals bijvoorbeeld enzymen in het menselijke lichaam. Het belang van enantiomeren kan geïllustreerd worden met het volgende voorbeeld; Ketamine kan gebruikt worden als een narcosemiddel, mits het juiste enantiomeer wordt toegediend. Het andere enantiomeer werkt echter als een hallucinerend middel (zie inzet). Voor biologisch actieve verbindingen, zoals geneesmiddelen, is het dus van belang dat slechts een enantiomeer gebruikt wordt.



(*R*)-Ketamine
Hallucinerend

(*S*)-Ketamine
Verdovend



Enantiomeren kunnen onder andere verkregen worden door chemische reacties. Normaal gesproken is een chemische reactie niet selectief en zal er evenveel van beide enantiomeren worden gevormd. Een mogelijkheid om een reactie te beïnvloeden, zodat maar een van beide enantiomeren wordt gevormd, is door het toevoegen van een kleine hoeveelheid chirale katalysator. De katalysatoren die in dit proefschrift beschreven zijn bestaan uit een metaal (rhodium) dat omringd wordt door twee chirale liganden, dwz chirale monodentaat fosforamidieten. Deze monodentaat fosforamidieten zijn organische moleculen die een fosfor atoom bevatten die omringd wordt door twee zuurstof atomen en één stikstof atoom. Ze zijn monodentaat, omdat ze maar met een positie aan het metaal gecoördineerd zijn. Monodentaat liganden veranderen de eigenschappen van het metaal en zorgen ervoor dat het metaal in oplossing blijft. Nu is het niet zo dat bij het gebruik van

een chirale katalysator in een chemische reactie er altijd maar één enantiomeer wordt gevormd. De selectiviteit van een katalysator wordt uitgedrukt in e.e. naar het Engelse enantiomeric excess (= enantiomere overmaat). 0% komt overeen met een gelijke verhouding van beide enantiomeren en 100% met de aanwezigheid van uitsluitend één van beide enantiomeren.

Dit proefschrift gaat over het ontwikkelen van nieuwe homogene* katalysatoren die gebruikt worden om chirale, enantiomeer zuivere, verbindingen te maken d.m.v. hydrogeneringsreacties.

Inhoud van dit proefschrift

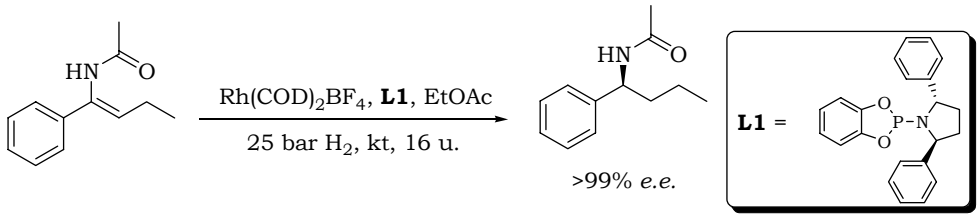
In hoofdstuk 1 wordt een inleiding gegeven over chiraliteit, gevolgd door een kort historisch overzicht van de ontwikkelingen in het veld van de asymmetrische hydrogeneringen en de huidige stand van zaken in de asymmetrische hydrogenering met monodentaat liganden. Tot een aantal jaren geleden werden voornamelijk bidentaat liganden gebruikt in de asymmetrische katalyse. Doordat monodentaat liganden over het algemeen eenvoudig kunnen worden gesynthetiseerd, is het relatief eenvoudig in de structuur van deze liganden kleine veranderingen aan te brengen. Bidentaat† liganden daarentegen zijn over het algemeen moeilijker te synthetiseren, wat variatie van deze liganden ingewikkelder maakt. Dit, gecombineerd met het feit dat monodentaat liganden even goede resultaten geven als bidentaat liganden in diverse asymmetrische katalyse processen, heeft er voor gezorgd dat er de laatste zes jaar een stroomversnelling heeft plaats gevonden in de ontwikkeling van monodentaat liganden. Het hoofdstuk eindigt met een overzicht van de laatste twee jaren op het gebied van asymmetrische katalyse met monodentaat liganden. Vanwege de grote aantal publicaties wordt dit overzicht beperkt tot het gebruik van monodentaat fosforamidieten in de asymmetrische katalyse.

De meeste succesvolle chirale monodentaat liganden die gebruikt worden in de asymmetrische hydrogenering zijn gebaseerd op een chirale backbone. In hoofdstuk 2 worden de eerste voorbeelden gegeven van monodentaat fosforamidieten die gebaseerd zijn op een achirale backbone. Deze catechol-gebaseerde liganden geven uitstekende resultaten in de asymmetrische hydrogenering van een tal van substraten. Een voorbeeld is gegeven in Schema 1.

---

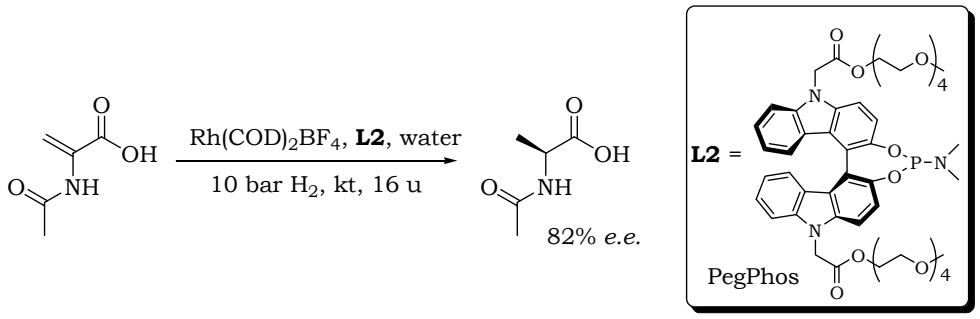
* Homogeen wil zeggen dat de katalysator oplosbaar is in het reactiemedium

† Bidentaat betekent dat deze liganden met twee posities aan het metaal gecoördineerd zijn.



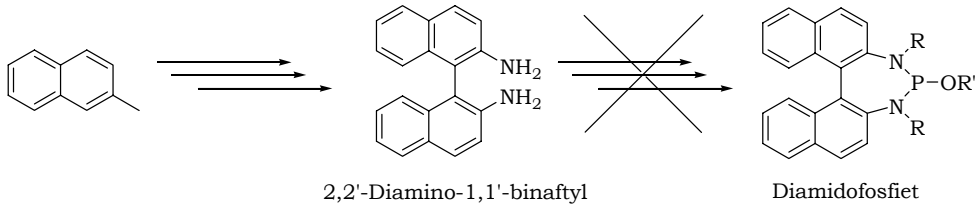
Schema 1: Asymmetrische hydrogenering met fosforamidiet **L1**.

Voor hydrogeneringen worden meestal organische oplosmiddelen gebruikt. Water wordt zelden gebruikt, omdat veel katalysatoren niet oplosbaar of stabiel zijn in water. In hoofdstuk 3 wordt de synthese en het gebruik van het eerste wateroplosbare monodentaat fosforamidiet, PegPhos (L2), beschreven (Schema 2).



Schema 2: Asymmetrische hydrogenering met PegPhos (**L2**) in water.

Monodentaat fosforamidieten zijn uitstekende liganden voor o.a. rhodium-gekatalyseerde hydrogeneringen. Monodentaat diamidofosfieten daarentegen worden zelden beschreven als liganden voor asymmetrische katalyse. In hoofdstuk 4 wordt de synthese van 2,2'-diamino-1,1'-binaftyl beschreven en de poging om hieruit monodentaat diamidofosfiet liganden te maken (Schema 3).

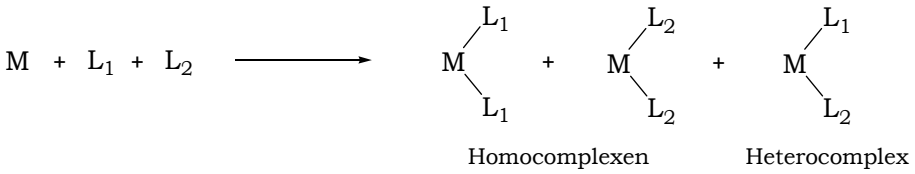


Schema 3: Poging tot synthese van diamidofosfieten.

In hoofdstuk 5 wordt de asymmetrische hydrogenering van onverzadigde carbonzuren besproken. Er werd gebruik gemaakt van een monodentaat ligand

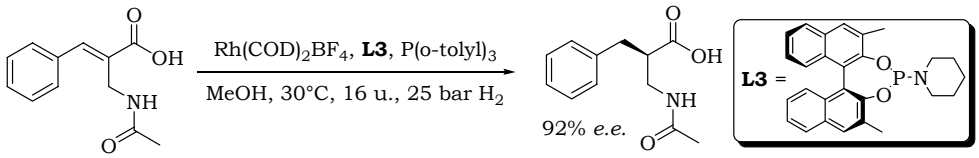
combinatie methode, waarbij twee verschillende monodentaat liganden i.p.v. twee identieke liganden gebruikt wordt. Hierbij ontstaat een mengsel van drie katalysatoren, d.w.z. 2 homocomplexen (2 identieke liganden gecomplexeerd aan het metaal) en 1 heterocomplex (2 verschillende liganden gecomplexeerd aan het metaal) (Schema 4). Wanneer het heterocomplex sneller en selectiever is dan de homocomplexen leidt dit tot betere resultaten.

De in dit hoofdstuk beschreven combinatie van liganden bestaat uit een chiraal fosforamidiet en een achiraal fosfine. Het is opmerkelijk dat het toevoegen van een achiraal ligand zowel de reactiesnelheid als de enantioselectiviteit van de reactie toeneemt. De formatie van de heterocomplexen is aangetoond met ^{31}P-NMR spectroscopie. De verkregen producten zijn interessante tussenproducten voor o.a. moleculaire motoren en geneesmiddelen.



Schema 4: De monodentaat ligand combinatie methode.

De monodentaat ligand combinatie methode, gebruik makend van een combinatie van een chiraal fosforamidiet en een achiraal fosfine, is tevens toegepast in de hydrogenering van β^2-dehydroamino zuren. Ligand optimalisatie is uitgevoerd door het parallel screenen van verschillende liganden m.b.v. een geautomatiseerd systeem. Enantioselectiviteiten tot 92% zijn bereikt (Schema 5). De resultaten staan beschreven in hoofdstuk 6.

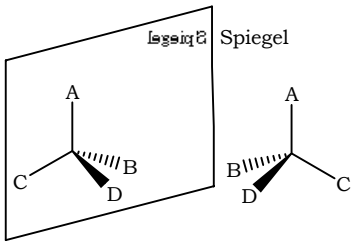


Schema 5: Asymmetrische hydrogenering van *β*^{2}-dehydroamino zuren.

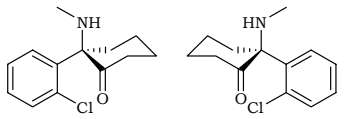
In hoofdstuk 7 wordt de synthese en screening van phenol-gebaseerde fosforamidieten beschreven. De synthese en screening zijn gedaan m.b.v. een geautomatiseerd systeem. In de meeste gevallen werden goede reactiviteiten gevonden. De enantioselectiviteiten waren echter in alle gevallen laag. De formatie van liganden werd bestudeerd met behulp van ^{31}P-NMR spectroscopie, waarbij geobserveerd werd dat de meeste phenol-gebaseerde liganden gevormd werden.

Zusammenfassung

Neue Methoden zur asymmetrischen Rhodium-katalysierten Hydrierung unter Verwendung von monodentaten Phosphoramiditen

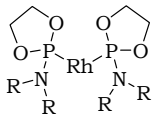


Moleküle sind räumliche Strukturen von Atomen. Kohlenstoff (C) ist eines der am häufigsten in der Natur vorkommenden Atome. Kohlenstoff ist vierbinding, d.h. er hat bis zu vier Substituenten, die gemeinsam mit dem zentralen Kohlenstoffatom einen Tetraeder bilden. Falls diese vier Substituenten unterschiedlich sind, sind zwei verschiedene Strukturen möglich. Diese beiden Strukturen sind Spiegelbilder und können nicht ineinander überführt werden. Man bezeichnet solche Moleküle als chiral oder asymmetrisch. Die beiden Spiegelbilder werden auch Enantiomere genannt. Enantiomere haben die selben physikalischen Eigenschaften, d.h. Siedepunkt, Schmelzpunkt, Molekulargewicht usw.. Die einzigen Unterschiede sind die optische Aktivität und die Wechselwirkung mit anderen chiralen Molekülen, wie den Enzymen im menschlichen Körper. Die Bedeutung von chiralen Molekülen kann durch folgendes Beispiel verdeutlicht werden: Ein Enantiomer des Ketamins kann als Anestetikum verwendet werden. Das andere Enatiomer hingegen hat halluzinogene Eigenschaften. Dieses Beispiel zeigt, wie wichtig es ist, daß nur ein Enantiomer von biologisch aktiven Substanzen verwendet wird.



(*R*)-Ketamin
Hallucinogen

(*S*)-Ketamin
Anästhetikum



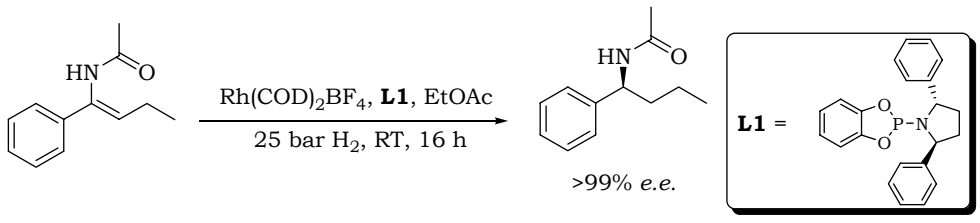
Eine Möglichkeit nur ein Enantiomer zu erhalten, bieten chemische Reaktionen. Normalerweise sind chemische Reaktionen nicht selektiv und beide Enantiomere werden in gleicher Menge gebildet. Man kann die Reaktion aber durch Zugabe eines chiralen Katalysators so beeinflussen, daß nur eines der beiden Enantiomere entsteht. Die Katalysatoren, die in dieser Arbeit beschrieben werden, bestehen aus einem Metallzentrum (Rhodium), welches durch zwei chirale Liganden (z.B. chirale monodentate Phosphoramidite) umgeben ist. Diese monodentaten Phosphoramidite sind organische Verbindungen und beinhalten ein Phosphoratom, das an zwei Sauerstoffatome und ein Stickstoffatom gebunden ist. Sie werden als Monodentate bezeichnet, da diese Liganden nur mit einer Position an das zentrale Metallatom koordinieren. Monodentate Liganden verändern die Eigenschaften des Metalls und bewirken so, daß das Metall in Lösung bleibt. Die

Verwendung eines chiralen Katalysators in einer chemischen Reaktion bedeutet aber nicht automatisch, daß nur ein Enantiomer gebildet wird. Die Selektivität des Katalysators kann als *e.e.* (*Enantiomerenüberschuß)* des gebildeten chiralen Produktes ausgedrückt werden. Ein *e.e.* von 0% bedeutet, daß beide Enantiomere in gleicher Menge vorliegen, wohingegen ein *e.e.* von 100% besagt, daß nur ein Enantiomer vorliegt.

Diese Arbeit beschreibt die Entwicklung von neuen homogenen* Katalysatoren zur Herstellung chiraler Verbindungen durch asymmetrische Hydrierung.

Inhalt der Arbeit

Im ersten Kapitel wird eine Einführung in die Thematik der Chiralität gegeben, gefolgt von einem kurzen geschichtlichen Überblick über die Entwicklung der homogenen asymmetrischen Hydrierung und einem Überblick über die Verwendung von monodentaten Liganden. Bis vor wenigen Jahren wurden hauptsächlich bidentaten Liganden† in der asymmetrischen Katalyse eingesetzt. Variationen in der Struktur der monodentaten Liganden sind durch ihre gradlinige Synthese einfach zu realisieren. Variationen in der Struktur von bidentaten Liganden hingegen sind oft schwer zugänglich. Dies, in Kombination mit der Tatsache, daß monodentate Liganden gleich gute Ergebnisse in vielen asymmetrisch katalysierten Reaktionen erzielen, hat zur Entwicklung vieler Monodentatliganden in den letzten sechs Jahren geführt. Das Kapitel endet mit einem Überblick über die Verwendung von monodentaten Liganden in der asymmetrischen Katalyse in den letzten beiden Jahren. Aufgrund der großen Anzahl von Publikationen auf diesem Gebiet wurde die Übersicht auf die Verwendung von monodentaten Phosphoramiditen beschränkt.



Schema 1: Asymmetrische Hydrierung mit Phosphoramidit **L1**.

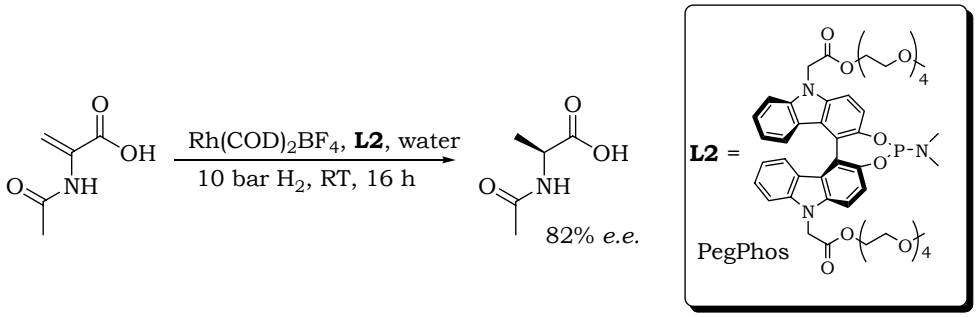
Die am erfolgreichsten bei der asymmetrischen Hydrierung eingesetzten monodentaten Liganden basieren auf einem chiralen Rückgrat. Die ersten

* Homogen bedeutet, daß der Katalysator im Reaktionsmedium löslich ist.

† Bidentat bedeutet, daß der Ligand mit zwei Positionen an das Metall koordiniert.

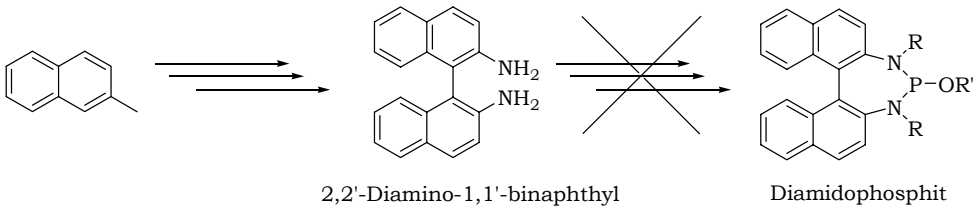
Beispiele zur Synthese und Verwendung von monodentaten Phosphoramiditen mit einem achiralen Catecholrückgrat werden in Kapitel 2 behandelt. Diese catecholbasierten Liganden erzielten exzellente Ergebnisse bei der asymmetrischen Hydrierung einer großen Anzahl von Substraten. Ein Beispiel wird in Schema 1 gegeben.

Im Allgemeinen werden organische Lösungsmittel für Hydrierungsreaktionen verwendet. Wasser wird selten verwendet, da viele Katalysatoren in Wasser nicht löslich oder nicht stabil sind. Die Synthese und Anwendung des ersten wasserlöslichen monodentaten Phosphoramidits, PegPhos (**L2**), wird in Kapitel 3 beschrieben (Schema 2).



Schema 2: Asymmetrische Hydrierung mit PegPhos (**L2**) in Wasser.

Monodentate Phosphoramidite sind exzellente Liganden für die Rhodium-katalysierte Hydrierung. Allerdings werden die monodentaten Phosphoramidite bislang kaum in der asymmetrischen Katalyse verwendet. Kapitel 4 beschreibt die Synthese von 2,2'-Diamino-1,1'-binaphthyl und die Versuche daraus ein monodentates Diamidophosphit darzustellen (Schema 3).

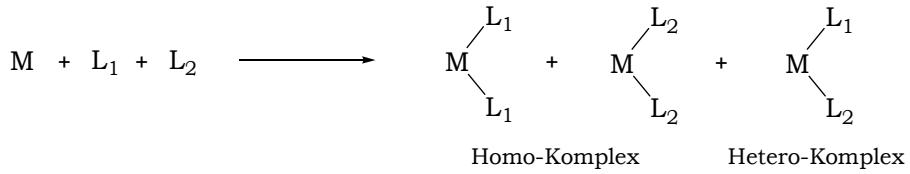


Schema 3: Versuchte Synthese eines Diamidophosphits.

Die asymmetrische Hydrierung von ungesättigten Carbonsäuren unter Verwendung von monodentaten Ligandmischungen wird in Kapitel 5 beschrieben. Hierbei wird eine Kombination von zwei verschiedenen monodentaten Liganden verwendet. Bei Verwendeung von zwei verschiedenen monodentaten liganden

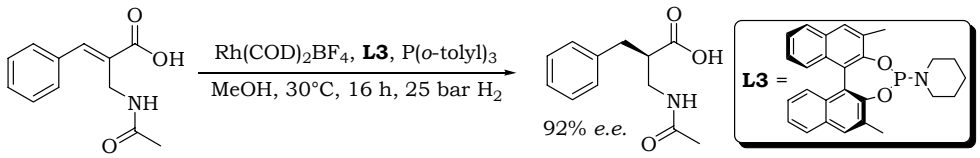
erhält man eine Mischung von drei Katalysatoren, d.h. zwei Homo-Komplexe (zwei identische Liganden koordinieren an das Metall) und ein Hetero-Komplex (zwei verschiedene Liganden koordinieren an das Metall) (Schema 4). Dies führt zu besseren Ergebnissen, wenn der Hetero-Komplex eine höhere Aktivität und eine höhere Selektivität zeigt als der vergleichbare Homo-Komplex.

Die in diesem Kapitel beschriebene Ligandenkombination besteht aus einem chiralen Phosphoramidit und einem achiralen Phosphin. Bemerkenswert ist, daß die Zugabe eines achiralen Liganden die Reaktivität wie auch die Enantioselektivität erhöht. Die Bildung des Hetero-Komplexes konnte durch ^{31}P-NMR bewiesen werden. Die in diesen Reaktionen erhaltenen Produkte sind interessante Intermediate z.B. für die Synthese von Naturstoffen oder Medikamenten.



Schema 4: Verwendung von Ligandmischungen.

Die Verwendung von Ligandmischungen aus chiralen Phosphoramiditen und achiralen Phosphinen wurde auch bei der asymmetrischen Hydrierung von *β*^{2}-Dehydroaminosäuren (siehe Schema 5) getestet. Die Ligandoptimierung wurde automatisch durchgeführt. Enantioselektivitäten von bis 92% konnten dabei erzielt werden. Die Ergebnisse werden in Kapitel 6 diskutiert.

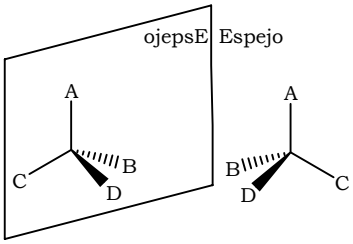


Schema 5: Asymmetrische Hydrierung von *β*^{2}-Dehydroaminosäuren.

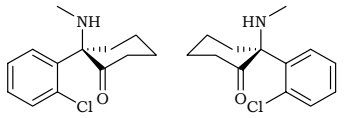
Die Synthese und das Screening von Phenol-basierten Phosphoramiditen, ebenfalls unter Verwendung eines automatischen Systems, wird in Kapitel 7 beschrieben. In den meisten Fällen können gute Reaktivitäten beobachtet werden. Die Enantioselektivitäten hingegen sind gering. Die Bildung der Liganden wird mittels ^{31}P-NMR-Spektroskopie beobachtet, die zeigt, daß in den meisten Fällen Phenol-basierte Phosphoramidite gebildet werden.

Resumen

NUEVOS CATALIZADORES DE RODIO QUE POSEEN LIGANDOS FOSFORAMIDITOS MONODENTADOS PARA LA OBTENCIÓN DE COMPUESTOS QUIRALES VIA HIDROGENACIONES ASIMÉTRICAS

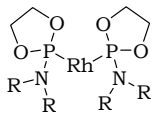


Las moléculas son estructuras espaciales de los átomos. El carbono es uno de los átomos más abundantes de la naturaleza. El carbono puede tener como máximo cuatro sustituyentes, los cuales junto con el carbono central forman una estructura tetraédrica. Cuando estos cuatro sustituyentes son diferentes, es posible formar dos estructuras distintas que son imágenes especulares y que por lo tanto no se pueden superponer. De modo que cada una de estas estructuras se consideran asimétricas o quirales. Las dos estructuras que son imágenes especulares se denominan enantiómeros. Los enantiómeros tienen las mismas propiedades físicas, como por ejemplo, el punto de ebullición, el punto de fusión, el peso molecular, etc. Sin embargo, se diferencian en la actividad óptica o en su interacción con otras moléculas quirales, como por ejemplo los enzimas en el cuerpo humano. La importancia de las moléculas quirales se ve reflejada en el siguiente ejemplo; la Ketamina se puede usar como anestésico si se administra el enantiómero correcto, sin embargo la administración del otro enantiómero tiene propiedades alucinógenas. Este ejemplo nos muestra lo importante que puede ser el poder usar uno solo de los enantiómeros del compuesto biológicamente activo.



(*R*)-Ketamina
Alucinógeno

(*S*)-Ketamina
Anestésico

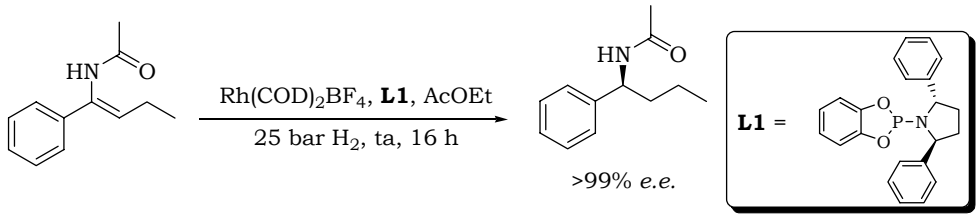


Una manera de obtener enantiómeros es vía reacciones químicas. Normalmente las reacciones químicas no son selectivas, lo que supone que se obtendrán los dos enantiómeros en cantidades equimolares. Una manera de favorecer que en una reacción química se forme uno de los enantiómeros es añadiendo una pequeña cantidad de un catalizador quiral. Los catalizadores descritos en esta tesis consisten en un metal (Rodio) que está rodeado por ligandos quirales, en concreto fosforamiditos quirales monodentados. Los fosforamiditos monodentados son moléculas orgánicas que poseen un átomo de fósforo unido a dos átomos de oxígeno y a un átomo de nitrógeno. La denominación de monodentados es debido a que estos ligandos sólo se coordinan al metal a través de una posición. Los ligandos monodentados se unen al metal cambiando así sus propiedades, como por ejemplo, haciendo que el metal sea estable en disolución. El uso de un catalizador quiral en una reacción química no implica que automáticamente se forme un solo enantiómero. La selectividad de un catalizador viene expresada en e.e. (exceso enantiomérico) del producto quiral formado. Un e.e. del 0% corresponde a una cantidad equimolar de

los dos enantiómeros, mientras que un e.e. del 100% corresponde a la presencia exclusiva de uno de los dos enantiómeros. Esta tesis describe el desarrollo de nuevos catalizadores homogéneos* para su uso en la obtención de compuestos quirales a través de hidrogenaciones asimétricas.

CONTENIDOS DE LA TESIS

En el capítulo 1 se presenta una introducción sobre quiralidad, seguida de una pequeña descripción histórica de los conocimientos en el campo de las hidrogenaciones asimétricas homogéneas, así como de la importancia del uso de ligandos monodentados. Hasta hace unos años, en catálisis asimétrica se usaban principalmente ligandos bidentados.† Las ventajas que supone el usar ligandos monodentados frente al uso de ligandos bidentados se basa principalmente en que los ligandos monodentados se pueden modificar fácilmente ya que su síntesis es muy directa. En cambio, las modificaciones en la estructura de los ligandos bidentados son en general más difíciles. Además de esta ventaja, se ha observado que los ligandos monodentados dan buenos resultados en muchas reacciones de catálisis asimétrica, de ahí que el desarrollo de nuevos ligandos monodentados haya aumentado en los últimos seis años. El capítulo termina con una descripción de las aplicaciones de los ligandos monodentados en catálisis asimétrica en los últimos dos años. Debido a la enorme cantidad de publicaciones que existen en este campo, este capítulo se limita a describir el uso de ligandos fosforamiditos.



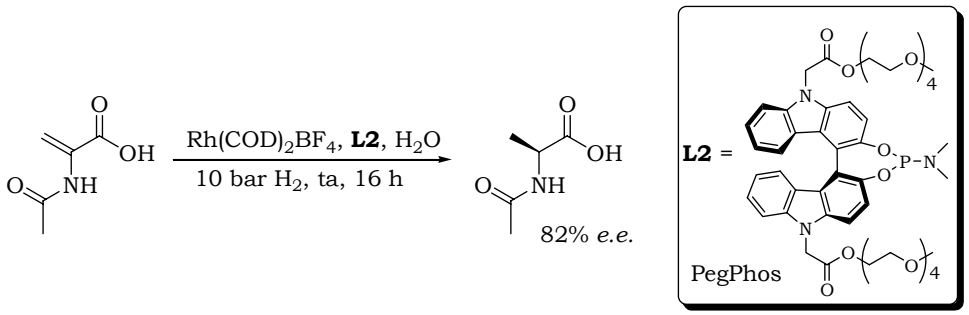
Esquema 1: Hidrogenación asimétrica con fosforamiditos **L1**.

Los ligandos monodentados con los que se han obtenido mejores resultados en las hidrogenaciones asimétricas son aquellos que poseen un esqueleto quiral. Los primeros ejemplos de la síntesis y el uso de fosforamiditos monodentados, presentados en el capítulo 2, poseen un esqueleto catecol aquiral. Estos ligandos derivados del catecol han dado muy buenos resultados en las hidrogenaciones asimétricas de un gran numero de sustratos, como en el ejemplo que se presenta en el Esquema 1.

* Homogéneo significa que el catalizador es soluble en el medio de reacción.

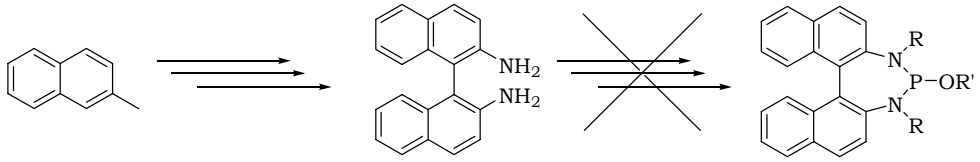
† Bidentado significa que el ligando esta coordinado al metal en dos posiciones

En general, las reacciones de hidrogenación se llevan a cabo en disolventes orgánicos ya que la mayoría de los catalizadores que se utilizan no son estables o no son solubles en disoluciones acuosas. Sin embargo en el capítulo 3 se describe la síntesis y aplicaciones de los primeros fosforamiditos monodentados solubles en agua, PegPhos (**L2**) (Esquema 2).



Esquema 2: Hidrogenación asimétrica con PegPhos (**L2**) en agua.

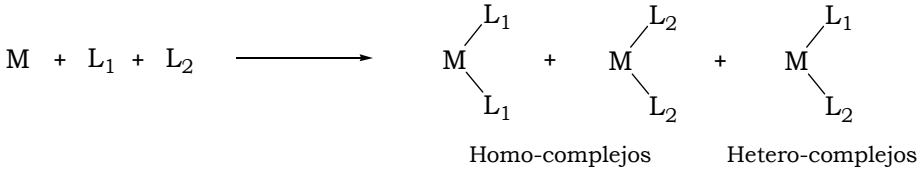
Los fosforamiditos monodentados son unos ligandos excelentes para las hidrogenaciones catalizadas por Rodio. Sin embargo, los diamidofosfitos monodentados apenas se han utilizado como ligandos en catálisis asimétrica. Por lo tanto, en el capítulo 4 se describe la síntesis del 2,2'-diamino-1,1'-binaftilo y su uso en la obtención de diamidofosfitos monodentados (Esquema 3).



Esquema 3: Ruta sintética para la síntesis de diamidofosfitos.

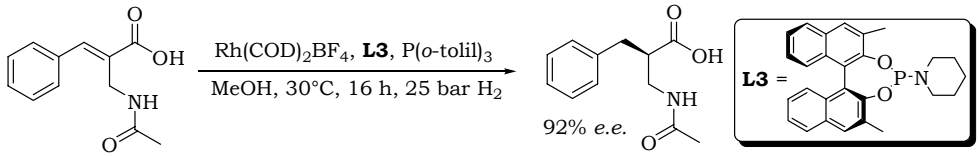
En el capítulo 5 se describe la hidrogenación asimétrica de ácidos carboxílicos insaturados, usando la estrategia de los ligandos monodentados combinados. En esta estrategia se utilizan dos ligandos monodentados diferentes en lugar de dos idénticos. Cuando utilizamos la combinación de dos ligandos monodentados diferentes entonces obtenemos una mezcla de tres catalizadores, dos homo-complejos (2 ligandos idénticos unidos al metal) y un hetero-complejo (2 ligandos diferentes unidos al metal) (Esquema 4). Este método nos proporcionará mejores resultados en las reacciones catalíticas siempre y cuando el hetero-complejo permita obtener mayores rendimientos y selectividades que el homo-complejo correspondiente.

La combinación de ligandos, tratada en este capítulo, consiste en un fosforamidito quiral y una fosfina aquiral. Sorprendentemente, la adición de un ligando aquiral al fosforamidito quiral aumenta la conversión así como la enantioselectividad del producto. La formación de los hetero-complejos ha sido confirmada por espectroscopia ^{31}P-NMR. Los productos obtenidos tienen interesantes aplicaciones, por ejemplo, en la generación de motores moleculares o en el campo de la medicina, entre otros.



Esquema 4: Estrategia para la obtención de ligandos monodentados combinados.

Además, estos ligandos monodentados combinados han sido utilizados en las hidrogenaciones asimétricas de β^2-aminoácidos (Esquema 5). La optimización y selección de los ligandos más satisfactorios para estas hidrogenaciones se ha llevado a cabo en un equipo automatizado, en el que se han observado enantioselectividades de hasta un 92 %. Estos resultados se presentan en el capítulo 6.



Esquema 5: Hidrogenación asimétrica de β^2-aminoácidos.

En el capítulo 7 se describe la síntesis y análisis, incluyendo la selección, de ligandos fosforamiditos basados en grupos fenol, usando un equipo automatizado. La formación de estos ligandos ha sido confirmada por análisis espectroscópico de ^{31}P-NMR. En la mayoría de los casos la reactividad obtenida es buena incluso cuando las enantioselectividades son bajas.

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Het werk dat beschreven staat in hoofdstuk 3 is voortgekomen uit een prettige samenwerking met Jan van Maarseveen, Stephane Leleu en Vanessa Appelman van de Universiteit van Amsterdam. De verkregen resultaten hebben uiteindelijk geresulteerd in een fraaie publicatie.

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I would like to thank all the (former) members of 14.223N, Bjorn, Christina, Chris, Hans, Jelle, Joost, Niek, Norbert and Wesley, for the nice working atmosphere in the lab. It has not always been easy for you to bear my broad taste of music.

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